

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-710

Administrative/Correspondence

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-710

NAME OF APPLICANT / NDA HOLDER

Shire Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

c 7

ACTIVE INGREDIENT(S)

Carbamazepine, USP

STRENGTH(S)

100 mg, 200 mg, 300 mg

DOSAGE FORM

Capsules

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,326,570

b. Issue Date of Patent

7/5/1994

c. Expiration Date of Patent

7/23/2011

d. Name of Patent Owner

Shire Laboratories, Inc.

Address (of Patent Owner)

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City/State

Rockville, MD

ZIP Code

20850

FAX Number (if available)

Telephone Number

301-838-2500

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3. N/A		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 18, 19, 20, 21, 22, 23, 24, 25	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Extended release carbamazepine for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

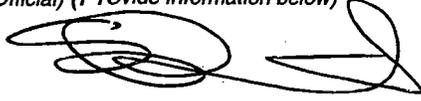
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



January 22, 2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

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The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



US005326570A

United States Patent [19]

[11] Patent Number: **5,326,570**

Rudnic et al.

[45] Date of Patent: **Jul. 5, 1994**

[54] **ADVANCED DRUG DELIVERY SYSTEM AND METHOD OF TREATING PSYCHIATRIC, NEUROLOGICAL AND OTHER DISORDERS WITH CARBAMAZEPINE**

[75] Inventors: Edward M. Rudnic, Gaithersburg; George W. Belendiuk, Potomac, both of Md.

[73] Assignee: Pharmavene, Inc., Gaithersburg, Md.

[21] Appl. No.: 734,541

[22] Filed: Jul. 23, 1991

[51] Int. Cl.⁵ A61K 9/54

[52] U.S. Cl. 424/458; 424/451; 424/452; 424/457; 424/459; 424/465; 424/468; 424/469; 424/489; 424/490

[58] Field of Search 424/451, 465, 457, 489, 424/459, 458, 468, 469, 490, 452; 544/152

[56] References Cited

U.S. PATENT DOCUMENTS

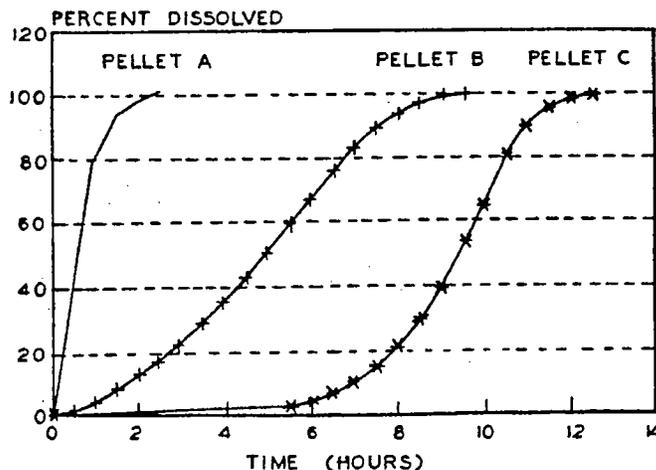
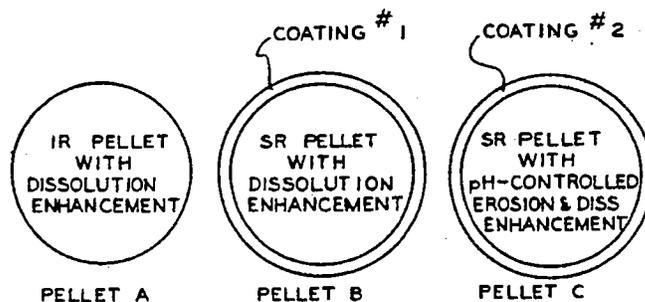
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Primary Examiner—Thurman K. Page
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Attorney, Agent, or Firm—Elliot M. Olstein; Susan A. Capello

[57] ABSTRACT

The present invention relates to a composition and method of treating a patient by administering carbamazepine in a pharmaceutical dosage form capable of maintaining the patient's blood concentration at from about 4 µg/ml to about 12 µg/ml over at least a 12 hour period, where the blood concentration of carbamazepine does not vary by more than 60 percent.

25 Claims, 1 Drawing Sheet



DOSAGE FORM COMPONENTS AND TARGET DISSOLUTION

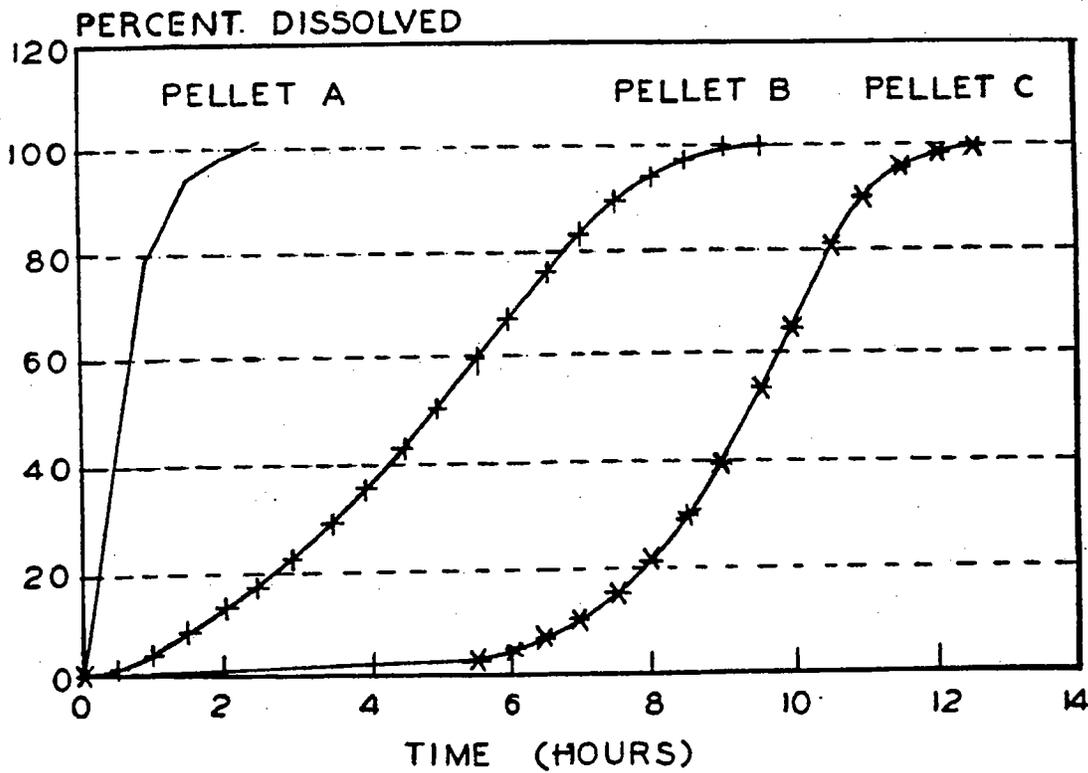
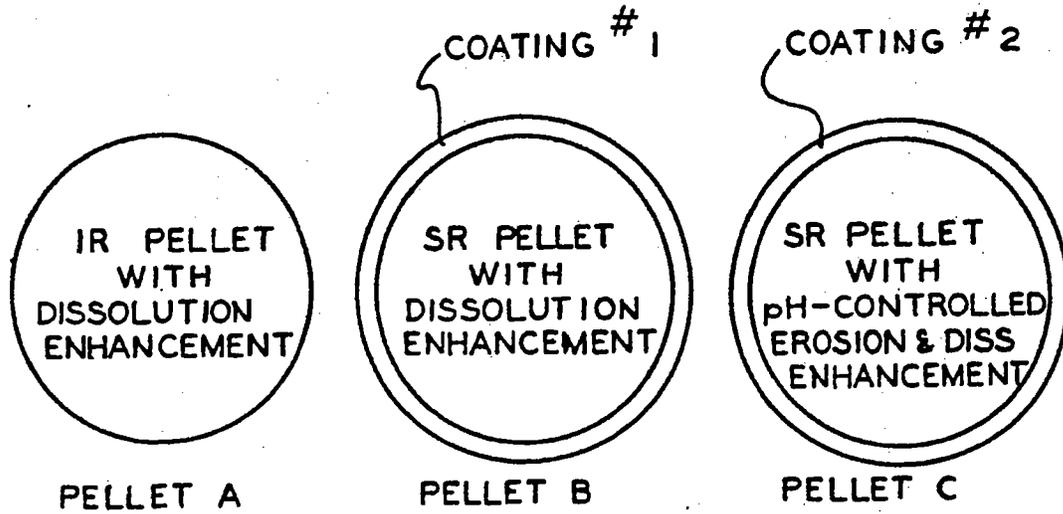


FIG. 1
DOSAGE FORM COMPONENTS
AND TARGET DISSOLUTION

**ADVANCED DRUG DELIVERY SYSTEM AND
METHOD OF TREATING PSYCHIATRIC,
NEUROLOGICAL AND OTHER DISORDERS
WITH CARBAMAZEPINE**

The present invention relates to a method of delivery for carbamazepine which will provide steady and consistent blood levels of carbamazepine. The blood levels of carbamazepine are within a therapeutic range required for the treatment of epilepsy as well as other psychiatric, neurological and other disorders.

Carbamazepine is an iminostilbene derivative that is used clinically to treat seizure disorders, trigeminal neuralgia, and most recently, manic depressive illness.

The present invention provides a method and composition for delivery of carbamazepine which provides steady and consistent blood levels of carbamazepine within a therapeutic range. The therapeutic range is from about 6 $\mu\text{g/ml}$ to about 12 $\mu\text{g/ml}$ of carbamazepine over a period of time. Blood levels of carbamazepine of less than 4 $\mu\text{g/ml}$ have been found to be ineffective in treating clinical disorders and blood levels greater than 12 $\mu\text{g/ml}$ have been found to be likely to result in undesirable side effects such as neuromuscular disturbances, cardiovascular and gastrointestinal effects.

The present invention provides for the maintenance of blood levels of carbamazepine (C) so as to minimize C_{max}/C_{min} variation or fluctuation. An acceptable fluctuation in the blood level C_{min}/C_{max} ratio would be a range of from about 0.6 to about 1.0. Most preferably, the variation or fluctuation would range from about 0.8 to about 1.0.

The present invention maintains a therapeutic range of blood levels of carbamazepine effective for the treatment of disorders which include but are not limited to depression, trigeminal; neuralgia; chronic pain states; headaches; addictive states for: cocaine, alcohol, opiates and nicotine; other obsessive compulsive disorders and cardiovascular disease.

An embodiment of the present invention provides for a sustained release method of delivery of carbamazepine which is to be administered at least once a day, preferably twice a day; therefore, in accordance with an aspect of the present invention there is provided a steady and consistent blood level of carbamazepine within therapeutic range of from about 4 $\mu\text{g/ml}$ to about 12 $\mu\text{g/ml}$, over a time period of at least 12 hours. In accordance with the present invention, within the hereinabove noted therapeutic range, the blood concentration of carbamazepine varies by not more than 60 percent and preferably by not more than 40 percent and most preferably by not more than 20% over a period of at least twelve hours.

The method of delivery of carbamazepine of the present invention provides for the following routes of administration sublingual, transmucosal, transdermal, parenteral and preferably oral. Parenteral administration would require an amount of carbamazepine of from about 100 mg to about 1000 mg per 12 hours. The dosage forms may include but are not limited to liquids, tablets, capsules, sprinkle dosage forms, chewable tablets and transdermal patches.

The sustained-release method of delivery of the present invention may be accomplished by administering multiple single unit dosage forms of equal or varying concentration of carbamazepine. Each such unit would

be designated to release its contents at varying times over at least a twelve hour time period so as to maintain a carbamazepine blood level within the therapeutic range previously described.

5 A preferred embodiment of the present invention provides for that the patient to be treated, ingest at a single point in time a dosage form containing carbamazepine capable of maintaining the patient's blood concentration at from about 4 $\mu\text{g/ml}$ to about 12 $\mu\text{g/ml}$ over at least a 12 hour time period, where the blood concentration of carbamazepine does not vary by more than 20%.

10 Such a dosage form may consist of one or more units, having the same or varying concentrations of carbamazepine, designed to release its contents at varying times so as to maintain a carbamazepine blood concentration level within the therapeutic range and for the time period previously described.

15 One preferred embodiment may comprise one single dosage form which contains multiple units within it, which are capable of releasing their contents at varying times. A second embodiment of the single dosage form, may also be to consist of one unit capable of immediately releasing a concentration of carbamazepine, then sustained-releasing carbamazepine at other time points as necessary to maintain blood levels within the therapeutic range. A third embodiment may be for the dosage form to be in multiple separate units capable of releasing carbamazepine at varying times, the separate multiple units as described above would all be ingested by the patient to be treated at the same time point.

20 Another embodiment of the present invention provides for a composition for treating a patient comprising an effective amount of carbamazepine and a pharmaceutically acceptable carrier which are sufficient for maintaining a blood concentration of carbamazepine within the therapeutic range and as described above.

25 Using either dosage form it is preferred that the dose of carbamazepine administered each 24 hour period is from about 800 mg to about 1200 mm. The dose is adjusted by the administering physician based upon the age, sex and weight of the patient to maintain therapeutic blood levels of carbamazepine.

30 Since carbamazepine is needed to be absorbed into the bloodstream over at least a twelve-hour period, it is preferred that the drug be administered in a dosage form that will reliably remain in the GI tract, in a sufficiently high region as to favor absorption.

35 To achieve and maintain the therapeutic range, a dose of from about 400 to about 600 mg per 12 hour period of carbamazepine makes it necessary to have a reasonably high loading of drug in the pellets. Because of this, it is preferred to have greater than 30% (W/W) of the pellet content as carbamazepine. It is preferable to have as great a concentration as possible, and therefore ideally as much as 95% (W/W) of each pellet would consist of the drug. It may not be practical to obtain this high loading of carbamazepine for all combinations of ingredients identified this application.

40 The term W/W as used herein is representative of a weight to weight ratio of the material specified to the weight of the unit dosage form as a whole.

45 For carbamazepine, it is preferred to have three different types of units in a single form multiple-unit dosage form. The first unit is an immediate release dosage form, preferably in pellet form. This component can also be a powder if necessary. In either case, the pellet should have a surface-active agent such as sodium lauryl sulfate, sodium monoglycerate, sorbitan monoole-

ate, polyoxyethylene sorbitan monooleate, glyceryl monostearate, glyceryl monooleate, glyceryl monobutyrate, any one of the Pluronic line of surface-active polymers, or any other suitable material with surface active properties or any combination of the above. Preferably the surface-active agent would be a combination of sodium monoglycerate and sodium lauryl sulfate. The concentration of these materials in this component can range from about 0.05 to about 10.0% (W/W).

The pellet should be made via a suitable process which makes the dosage form into a reasonably round unit. This process can be, for example, simple granulation, followed by sieving; extrusion and marumerization; roto granulation; or any agglomeration process which results in a pellet of reasonable size and robustness. As stated earlier, it is also possible to have this immediate release component as a powder, although the preferred form is a pellet due to mixing and de-mixing considerations.

The materials to be admixed along with the drug and surfactant for this first pellet should possess sufficient binding properties to allow agglomeration to occur. These materials can be, but are not limited to, microcrystalline cellulose (such as Avicel), corn starch, pregelatinized starch (such as Starch 1500 or National 1551), potato starch, sodium carboxymethylated starch, sodium carboxymethylated cellulose, hydroxypropylmethyl cellulose, hydroxypropylcellulose, hydroxyethylcellulose, ethylcellulose, as well as any cellulose ether. In addition, any binder material such as gums (ex. Guar Gum) natural binders and derivatives such as alginates, chitosan, gelatin and gelatin derivatives, are also useful. Synthetic polymers such as polyvinylpyrrolidone (PVP), acrylic acid derivatives (Eudragit, Carbopol, etc.) and polyethylene glycol (PEG) are also useful as binders and matrix formers for the purpose of this invention. It may be useful to have these materials present in the range of from about 1.0 to about 60.0% (W/W) either in total, or individually in combination with one another. Preferably, these materials should be present in the range of from about 30 to about 50 percent (W/W).

It may also be necessary to incorporate a disintegrant into these pellets in order to facilitate dissolution of the active ingredient. For this purpose, any suitable tablet disintegrant can be utilized here, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol), cross-linked sodium carboxymethyl starch (Explotab, Primogel), cross-linked PVP (Plasdone XL) or any other material possessing tablet disintegrant properties.

The second pellet should have a sustained release profile, and needs to be able to address the changing pH of the GI tract, and its effect on the absorption of carbamazepine. This pellet should have all of the ingredients as mentioned for pellet A, as well as some organic acid which will be useful to reduce the pH of the microenvironment of the pellet, and thus facilitate dissolution. These materials are, but not limited to, citric acid, lactic acid, tartaric acid, or other suitable organic acids. These materials should be present in concentrations of from about 0 to about 15.0% (W/W), preferably these materials would be present in concentrations of from about 5.0 to about 10.0 percent (W/W). The process for manufacturing these pellets is consistent to the process described above for the previous pellet.

In addition to the pellet, this component should have a controlling coat applied to the surface of the pellet such that the release of the drug from the pellet is con-

trolled and released over a 6-10 hour period. The materials used for this purpose can be, but are not limited to, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, nitrocellulose, carboxymethylcellulose, and any other cellulose ether, as well as copolymers of ethacrylic acid and methacrylic acid (Eudragit), or any other acrylic acid derivative (Carbopol, etc.) can be used. In addition, an enteric coating material can also be employed, either singularly, or in combination to the above non-pH sensitive coatings. These materials include, but are not limited to, hydroxypropylmethylcellulose phthalate and the phthalate esters of all the cellulose ethers. In addition, phthalate esters of the acrylic acid derivatives (Eudragit), or cellulose acetate phthalate. These coating materials can be employed in coating the surfaces in a range of from about 1.0% (W/W) to about 25% (W/W). Preferably these coating materials should be in a range of from about 8.0 to about 12.0 percent (W/W).

The third component in this system should be qualitatively similar to pellet B, in that the manufacturing process for producing this pellet is consistent with that of the first two pellets, and the microenvironment inside the pellet should be consistent with that of pellet B. However, this pellet should have some internal component for breaking down in the pH of the lower GI tract. Thus, it will be necessary to include some enteric or pH sensitive material into the pellet to facilitate erosion and breakdown in the lower GI tract. This material can be, but is not limited to, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, any additional cellulose ether phthalates, any of the acrylic acid derivative phthalates (Eudragit), as well as any enteric coating material, such as shellac, zein, or others. The concentration of these materials in the pellet should be from about 1.0 to about 15.0% (W/W), preferably the concentration of amaterials should be from about 5.0 to about 10.0 percent (W/W).

The coating of this third pellet should be similar to the coating for pellet B, except that it should have a considerable pH sensitivity associated with it. Therefore, it would be desirable to coat pellet C with any of the pH sensitive, or enteric coating materials listed above, either singularly, or in combination with any coating material mentioned above. The coating level of this pellet should range from about 1.0 to about 15.0% (W/W), preferably the concentration of materials should be from about 5.0 to about 12.0 percent (W/W).

BRIEF DESCRIPTION OF THE DRAWINGS

Each pellet should have its own dissolution profile associated with the formulation assigned to it. The target dissolution curves for the three pellets can be seen in FIG. 1.

This FIGURE shows a schematic of the three pellets, as well as the target dissolution for the materials. Depending on the formulation chosen in this invention, the exact ratios of each of the pellets may need to be adjusted. The amount of pellet A in the formulation should preferably range from about 5.0 to about 25.0%. The amount of Pellet B in the dosage form should range from about 15.0 to about 70.0%. The dosage form for Pellet C should be in a range of from about 10.0 to about 50.0%.

While the present invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and varia-

tions will be apparent to those skilled in the art in view of the foregoing description. Accordingly, the plenary invention is intended to embrace all such alternatives, modifications and variations as falling within the broadest scope and spirit of the described invention.

The following examples illustrate the invention in more detail without limiting the scope thereof.

EXAMPLES

The examples are presented in three groups, one for each pellet type as described above.

Pellet A: Immediate Release Component		
	Percent	Kilograms
Example 1:		
Microcrystalline Cellulose, N.F. (MCC) (Avicel PH-101/102, Emcoel, etc.)	40.0	0.4
Hydroxypropylmethylcellulose (HPMC) (Methocel E5/E50/K5/K50)	2.5	0.025
Croscarmellose, Type A, N.F. (Ac-Di-Sol)	2.0	0.02
Sodium Lauryl Sulfate (SLS)	0.1	0.001
Carbamazepine	55.4	0.554
Total	100.0	1.000
Example 2:		
MCC	40.0	0.4
HPMC	5.0	0.05
Sodium Starch Glycolate, N.F. (Explotab, Primojel)	8.0	0.08
SLS	0.3	0.003
Carbamazepine	46.7	0.467
Total	100.0	1.000
Example 3:		
MCC	20.0	0.2
Pre-gelatinized Starch (STARCH 1500, National 1551)	15.0	0.15
Croscarmellose	5.0	0.05
Corn Starch, U.S.P. (as paste)	5.0	0.05
Diocetyl Sodium Sulfosuccinate (DDS)	0.5	0.005
Carbamazepine	54.5	0.545
Total	100.0	1.000
Example 4:		
MCC	15.0	0.15
MCC/Carboxymethyl Cellulose (CMC) (Avicel RC Grade)	15.0	0.15
Croscarmellose	5.0	0.05
SLS	0.5	0.005
Carbamazepine	64.5	0.645
Total	100.0	1.000
Example 5:		
MCC/CMC	20.0	0.2
Croscarmellose	3.0	0.03
Sodium Starch Glycolate	5.0	0.05
HPMC	8.0	0.08
DDS	0.5	0.005
Carbamazepine	63.5	0.635
Total	100.0	1.000
Example 6:		
MCC	10.0	0.10
MCC/CMC	10.0	0.10
Croscarmellose	5.0	0.05
DDS	0.5	0.005
Carbamazepine	74.5	0.745
Total	100.0	1.000
Example 7:		
MCC/CMC	25.0	0.25
Polyacrylic Acid (Carbomer)	10.0	0.1
SLS	0.2	0.002
Sodium Starch Glycolate	7.5	0.075
Carbamazepine	57.3	0.573
Total	100.0	1.000
Example 8:		
MCC	30.0	0.30
HPMC	7.5	0.075
Croscarmellose	5.0	0.05

-continued

Sodium bis-(2-ethylhexyl)sulfosuccinate (Aerosol OT)	1.5	0.015
Carbamazepine	56.0	0.560
Total	100.0	1.000
Example 9:		
MCC	25.0	0.25
HPMC	5.0	0.05
Mono/Di/Tri-glyceride Mixture (Atmul-84S)	10.0	0.1
SLS	0.5	0.005
Carbamazepine	59.5	0.595
Total	100.0	1.000
Example 10:		
MCC	25.0	0.25
Polyvinylpyrrolidone (PVP) (Plasdone)	8.0	0.08
Sodium Monoglycerate (Myvalex)	8.0	0.08
SLS	0.35	0.0035
Carbamazepine	58.65	0.5865
Total	100.0	1.0000
Example 11:		
MCC	30.0	0.3
HPMC	5.0	0.05
Sodium Monoglycerate	8.0	0.08
Tartaric Acid	5.0	0.05
SLS	0.2	0.002
Carbamazepine	51.8	0.518
Total	100.0	1.000
Coating:		
Ethacrylic/Methacrylic Acid Esters (Eudragit RS100)	45.0	0.45
Ethacrylic/Methacrylic Acid Esters (Eudragit RL100)	45.0	0.45
Propylene Glycol	9.0	0.09
Talc	1.0	0.01
Total	100.0	1.00
Example 12:		
Same core pellet as in example 11		
Coating:		
HPMC (Methocel E50)	45.0	0.45
Ethylcellulose (Ethocel)	45.0	0.45
Polyethylene Glycol 400 (PEG400)	10.0	0.10
Total	100.0	1.00
Example 13:		
Same core pellet as in example 11		
Coating:		
HPMC	20.0	0.20
Ethylcellulose	70.0	0.70
PEG400	10.0	0.10
Total	100.0	1.00
Example 14:		
MCC	15.0	0.15
MCC/CMC Mixture	15.0	0.15
Citric Acid	6.0	0.06
DSS	0.8	0.008
Carbamazepine	63.2	0.632
Total	100.0	1.000
Coating:		
HPMC (Methocel K5M)	10.0	0.10
HPMC (Methocel E50)	14.0	0.14
Ethylcellulose	66.0	0.66
PEG400	10.0	0.10
Total	100.0	1.00
Example 15:		
Core pellet from example 14		
Coating from example 11		
Example 16:		
Core pellet from example 14		
Coating from example 12		
Example 16:		
Core pellet from example 14		
Coating from example 13		
Example 17:		
MCC	30.0	0.3
PVP	8.0	0.08
Mono/Di/Tri-Glyceride Mixture	8.0	0.08

-continued

SLS	0.3	0.003
Tartaric Acid	7.5	0.075
Carbamazepine	46.2	0.462
Total	100.0	1.000

Coating:

Coating from example 11

Example 18:

Core pellet from example 17

Coating from example 12

Example 19:

Core pellet from example 17

Coating from example 13

Core pellet from example 17

Coating from example 14

Pellet C: Delayed Release Component

Example 21:

Core Pellet:

	Percent	Kilogram
MCC	25.0	0.25
Hydroxypropylmethylcellulose	10.0	0.10
Phthalate (HPMCP)		
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Carbamazepine	47.0	0.470
Total	100.0	1.000

Coating:

Cellulose Acetate Phthalate (CAP)

Ethylcellulose

PEG400

Cellulose Acetate Phthalate (CAP)	60.0	0.60
Ethylcellulose	25.0	0.25
PEG400	15.0	0.15
Total	100.0	1.00

Example 22:

Core pellet from example 21

Coating:

Ethacrylic/Methacrylic Acid Esters (Eudragit line of enteric polymers)

Propylene Glycol

Talc

Ethacrylic/Methacrylic Acid Esters (Eudragit line of enteric polymers)	85.0	0.85
Propylene Glycol	14.0	0.14
Talc	1.0	0.01
Total	100.0	1.00

Example 23:

Core pellet from example 21

Coating:

CAP

HPMCP

PEG 400

PEG 8000

CAP	65.0	0.65
HPMCP	15.0	0.15
PEG 400	10.0	0.10
PEG 8000	10.0	0.10
Total	100.0	1.00

Core Pellet:

MCC

Mono/Di/Tri-glyceride Mixture

Tartaric Acid

CAP

DSS

Carbamazepine

MCC	25.0	0.25
Mono/Di/Tri-glyceride Mixture	15.0	0.15
Tartaric Acid	10.0	0.10
CAP	10.0	0.10
DSS	0.8	0.8
Carbamazepine	39.2	0.392
Total	100.0	1.000

Coating as in example 21

Example 25:

Core pellet as in example 24

Coating as in example 22

Example 26:

Core Pellet as in example 24

Coating as in example 23

Example 27:

Core pellet as in example 24

Coating:

Shellac

Mineral Oil

SLS

Talc

Shellac	85.0	0.85
Mineral Oil	13.0	0.13
SLS	0.5	0.005
Talc	1.5	0.015
Total	100.0	1.000

Example 28:

Core pellet as in example 21

Coating as in example 27

What is claimed is:

1. A drug delivery system for the oral administration of carbamazepine, comprising:
 - (a) a sustained release unit containing carbamazepine;
 - (b) an immediate release unit containing carbamazepine; and
 - (c) an enteric release unit containing carbamazepine, said combination of components (a), (b), and (c) containing a therapeutically effective amount of carbamazepine.
2. A method for treating a patient with carbamazepine, comprising: orally administering to the patient the system of claim 1.
3. The system of claim 1 wherein said components (a), (b) and (c) are present in a tablet.
4. The system of claim 1 wherein said components (a), (b) and (c) are present in a capsule.
5. The system of claim 1 wherein said components (a), (b) and (c) are present in a single dosage form.
6. The system of claim 1 wherein said components (a), (b), and (c) are in a pellet form and are present in a single dosage form.
7. The system of claim 6 wherein the single dosage form is a capsule.
8. The system of claim 1 wherein said system provides a therapeutically effective amount over a 12 hour period.
9. The system of claim 1 wherein said system comprising components (a), (b) and (c) contains carbamazepine in an amount from about 400 mg to about 600 mg.
10. The system of claim 1 wherein the system provides blood dosage levels of carbamazepine which do not vary by more than 60% over a 12 hour period.
11. The system of claim 10 wherein the blood dosage levels do not vary by more than 20% over a 12 period.
12. A system as in claim 1, wherein each of the units includes a surfactant.
13. A system as in claim 12, wherein the sustained release unit and the enteric release unit each contain an organic acid to maintain an acidic environment in the units.
14. A system as in claim 12, wherein said surfactant is sodium lauryl sulfate.
15. A system as in claim 1, wherein said sustained release unit is present in an amount ranging from about 5.0% to about 25.0% (w/w), said immediate release unit is present in an amount ranging from about 15.0% to about 70.0% (w/w) and said enteric release unit is present in an amount ranging from about 10.0% to about 50.0% (w/w).
16. A system as in claim 15, wherein said sustained release unit is coated with a coating material in an amount ranging from about 1.0% to about 25% (w/w) and said enteric release unit is coated with a coating material in an amount ranging from about 1.0% to about 15.0% (w/w).
17. A system as in claim 1, wherein the carbamazepine in said sustained release unit is released from said unit over a period from about 6 to about 10 hours.
18. A method of treating a patient with carbamazepine comprising: orally administering to said patient a composition which contains,
 - (a) an immediate release unit containing carbamazepine;
 - (b) a sustained release unit containing carbamazepine;
 - (c) an enteric release unit containing carbamazepine; said components (a), (b), and (c) containing a therapeutically effective amount of carbamazepine.

19. A method as in claim 18, wherein said components (a), (b), (c) being administered in a combined amount to maintain a blood dosage level of carbamazepine within a range of from about 4 µg/ml to about 12 µg/ml for a period of at least 12 hours.

20. A method as in claim 18, wherein the components being administered contain a combined amount of carbamazepine of from about 400 mg to about 600 mg.

21. A method as in claim 19, wherein the blood dosage level of carbamazepine does not vary by more than 60 percent per 12 hour period.

22. A method as in claim 20, wherein the blood dosage level of carbamazepine within said range does not vary by more than 20 percent per 12 hour period.

23. A method as in claim 18, wherein each of the units includes a surfactant.

24. A method as in claim 22, wherein said surfactant is sodium lauryl sulfate.

25. A method as in claim 23, wherein said sustained release unit and said enteric release unit each contain an organic acid to maintain an acidic environment in the units.

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**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
21-710
NAME OF APPLICANT / NDA HOLDER
Shire Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME) []	
ACTIVE INGREDIENT(S) Carbamazepine, USP	STRENGTH(S) 100 mg, 200 mg, 300 mg
DOSAGE FORM Capsules	

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 5,912,013	b. Issue Date of Patent 6/15/1999	c. Expiration Date of Patent 6/15/2016
d. Name of Patent Owner Shire Laboratories, Inc.	Address (of Patent Owner) 1550 East Gude Drive	
	City/State Rockville, MD	
	ZIP Code 20850	FAX Number (if available)
	Telephone Number 301-838-2500	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

.. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
N/A
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



January 22, 2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



US005912013A

United States Patent [19]

[11] Patent Number: **5,912,013**

Rudnic et al.

[45] Date of Patent: **Jun. 15, 1999**

[54] **ADVANCED DRUG DELIVERY SYSTEM AND METHOD OF TREATING PSYCHIATRIC, NEUROLOGICAL AND OTHER DISORDERS WITH CARBAMAZEPINE**

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[75] Inventors: **Edward M. Rudnic**, North Potomac; **George W. Belendiuk**, Potomac, both of Md.; **John McCarty**, Biscayne Park, Fla.; **Sandra Wassink**, Frederick; **Richard A. Couch**, Germantown, both of Md.

[73] Assignee: **Shire Laboratories, Inc.**, Rockville, Md.

[21] Appl. No.: **08/426,394**

[22] Filed: **Apr. 21, 1995**

Related U.S. Application Data

[63] Continuation of application No. PCT/US92/06123, Jul. 23, 1992, which is a continuation-in-part of application No. 07/734,541, Jul. 23, 1991, Pat. No. 5,326,570.

[51] Int. Cl.⁶ **A61K 47/32; A61K 9/22**

[52] U.S. Cl. **424/465; 424/468; 424/482; 424/489**

[58] Field of Search **424/489, 772.4, 424/465**

[56] References Cited

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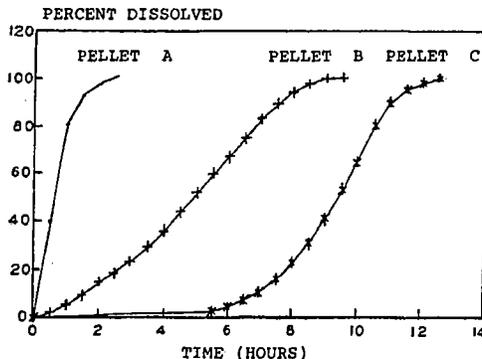
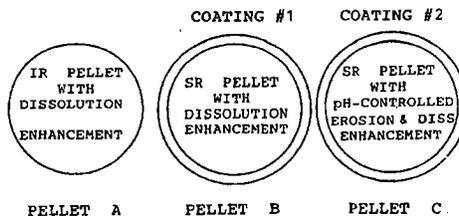
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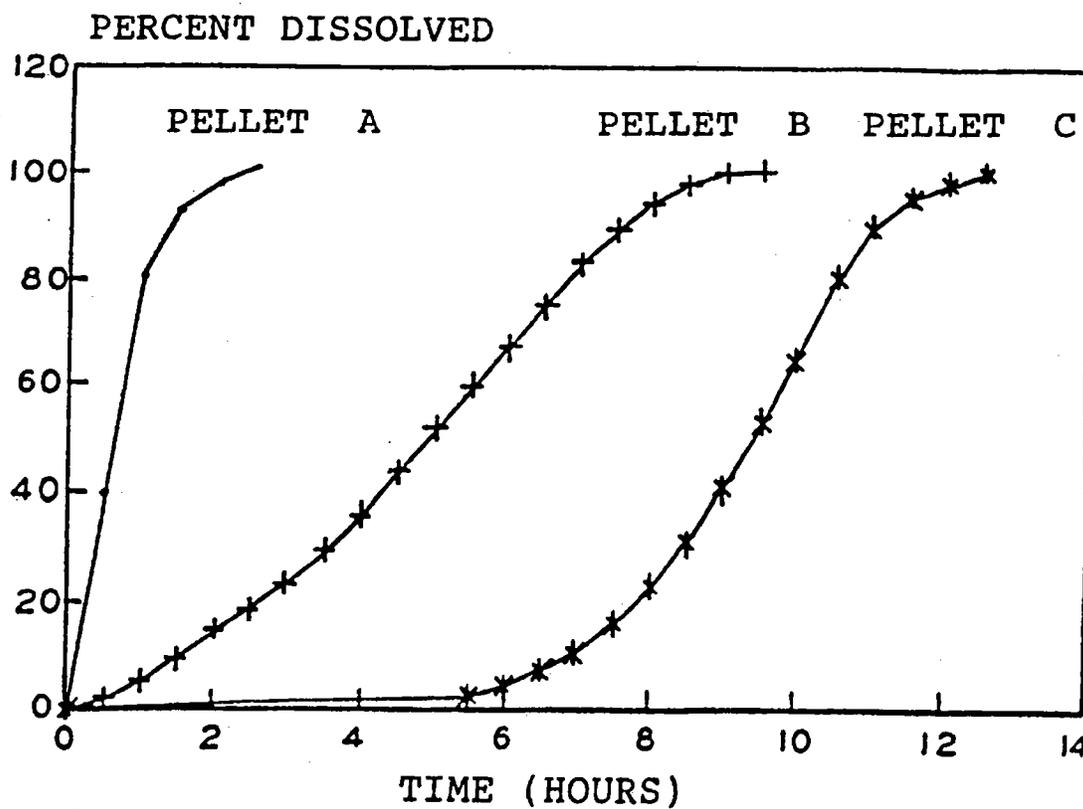
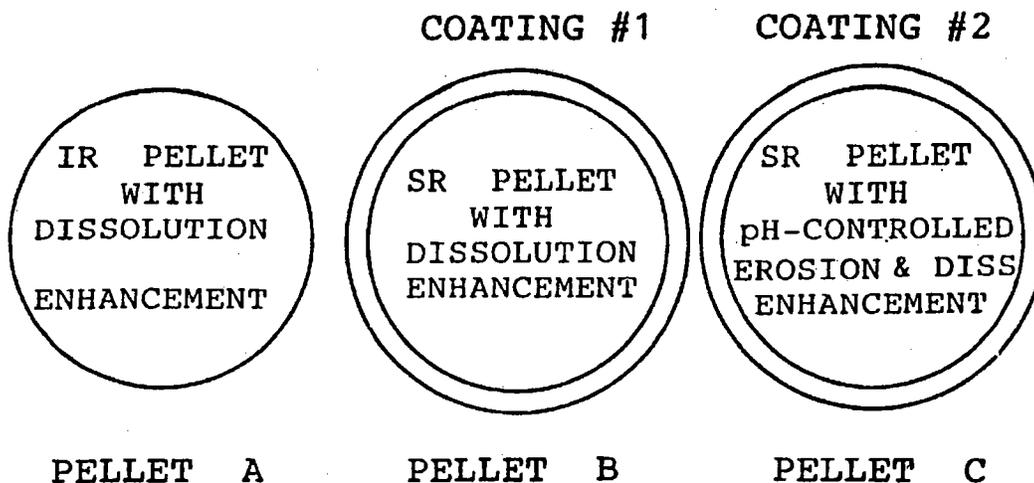
Primary Examiner—Peter F. Kulkosky
Attorney, Agent, or Firm—Elliot M. Olstein; Raymond J. Lillie

[57] ABSTRACT

The present invention relates to a composition and method of treating a patient by administering carbamazepine in a pharmaceutical dosage form capable of maintaining the patient's blood concentration at from about 4 µg/ml to about 12 µg/ml over at least a 12 hour period, where the blood concentration of carbamazepine does not vary by more than 60 percent.

10 Claims, 1 Drawing Sheet





**ADVANCED DRUG DELIVERY SYSTEM AND
METHOD OF TREATING PSYCHIATRIC,
NEUROLOGICAL AND OTHER DISORDERS
WITH CARBAMAZEPINE**

This application is a continuation of International Application No. PCT/US92/06123, filed Jul. 23, 1992, which is a continuation-in-part of Application Ser. No. 07/734,541, filed Jul. 23, 1991, now U.S. Pat. No. 5,326,570.

The present invention relates to a method of delivery for carbamazepine which will provide steady and consistent blood levels of carbamazepine. The blood levels of carbamazepine are within a therapeutic range required for the treatment of epilepsy as well as other psychiatric, neurological and other disorders.

Carbamazepine is an iminostilbene derivative that is used clinically to treat seizure disorders, trigeminal neuralgia, and most recently, manic depressive illness.

Carbamazepine is also known to those skilled in the art to be insoluble or difficult to solubilize. In addition, it is also difficult to achieve high loading of such a carbamazepine in a pellet form. The term high loading as used in this application shall mean at least sixty percent (60%) by weight of such carbamazepine. As used herein and as known in the art, the term robust pellets shall mean pellets capable of retaining their physical integrity during and after processing into a dosage form and undergoing standard coating procedures.

The present invention provides a method and composition for delivery of carbamazepine which provides steady and consistent blood levels of carbamazepine within a therapeutic range. The therapeutic range is from about 6 $\mu\text{g/ml}$ to about 12 $\mu\text{g/ml}$ of carbamazepine over a period of time. Blood levels of carbamazepine of less than 4 $\mu\text{g/ml}$ have been found to be ineffective in treating clinical disorders and blood levels greater than 12 $\mu\text{g/ml}$ have been found to be likely to result in undesirable side effects such as neuromuscular disturbances, cardiovascular and gastrointestinal effects.

The present invention provides for the maintenance of blood levels of carbamazepine (C) so as to minimize $C_{\text{max}}/C_{\text{min}}$ variation or fluctuation. An acceptable fluctuation in the blood level $C_{\text{min}}/C_{\text{max}}$ ratio would be a range of from about 0.6 to about 1.0. Most preferably, the variation or fluctuation would range from about 0.8 to about 1.0.

The present invention maintains a therapeutic range of blood levels of carbamazepine effective for the treatment of disorders which include but are not limited to depression, trigeminal; neuralgia; chronic pain states; headaches; addictive states for: cocaine, alcohol, opiates and nicotine; other obsessive compulsive disorders and cardiovascular disease.

An embodiment of the present invention provides for a sustained release method of delivery of carbamazepine which is to be administered at least once a day, preferably twice a day; therefore, in accordance with an aspect of the present invention there is provided a method for maintaining in a patient, steady and consistent blood level of carbamazepine within therapeutic range of from about 4 $\mu\text{g/ml}$ to about 12 $\mu\text{g/ml}$, over a time period of at least 12 hours. In accordance with the present invention, within the hereinabove noted therapeutic range, the blood concentration of carbamazepine varies by not more than 60 percent and preferably by not more than 40 percent and most preferably by not more than 20% over a period of at least twelve hours.

The method of delivery of carbamazepine of the present invention provides for the following routes of administration sublingual, transmucosal, transdermal, parenteral and preferably oral. Parenteral administration would require an

amount of carbamazepine of from about 100 mg to about 1000 mg per 12 hours. The dosage forms may include but are not limited to liquids, tablets, capsules, sprinkle dosage forms, chewable tablets, pellets and transdermal patches.

It is anticipated by this application that it may be possible to produce the pellets as described herein other than as robust pellets.

One aspect of the present invention provides for a sustained release method of delivery which includes administering one or more single unit dosage forms of equal or varying concentration of carbamazepine. Each such unit is designed to release its contents at varying times over at least a twelve hour time period so as to maintain a carbamazepine blood level within the therapeutic range previously described.

The term W/W as used herein is representative of a weight to weight ratio of the material specified to the weight of the unit dosage form as a whole.

To achieve and maintain the therapeutic range, a dose of from about 400 to about 600 mg per 12 hour period of carbamazepine is needed. Due to this, it is preferred to have greater than 30% (W/W) of the pellet content as carbamazepine. The following are representative examples of the various ingredients which may be included in the sustained-release formulation.

For carbamazepine, it is preferred to have three different types of units in a single form multiple-unit dosage form. The first unit is an immediate release dosage form, preferably in pellet form. This component can also be a powder if necessary. In either case, the pellet should have a surface-active agent such as sodium lauryl sulfate, sodium monoglycerate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, glyceryl monostearate, glyceryl monooleate, glyceryl monobutyrate, any one of the Pluronic line of surface-active polymers, or any other suitable material with surface active properties or any combination of the above. Preferably the surface-active agent would be a combination of sodium monoglycerate and sodium lauryl sulfate. The concentration of these materials in this component can range from about 0.05 to about 10.0% (W/W).

The pellet should be made via a suitable process which makes the dosage form into a reasonably round unit. This process can be, for example, simple granulation, followed by sieving; extrusion and marumerization; rotogranulation; or any agglomeration process which results in a pellet of reasonable size and robustness. As stated earlier, it is also possible to have this immediate release component as a powder, although the preferred form is a pellet due to mixing and de-mixing considerations.

The materials to be admixed along with the drug and surfactant for this first pellet should possess sufficient binding properties to allow agglomeration to occur. These materials can be, but are not limited to, microcrystalline cellulose (such as Avicel), corn starch, pregelatinized starch (such as Starch 1500 or National 1551), potato starch, sodium carboxymethylated starch, sodium carboxymethylated cellulose, hydroxypropylmethyl cellulose, hydroxypropylcellulose, hydroxyethylcellulose, ethylcellulose, as well as any cellulose ether. In addition, any binder material such as gums (ex. Guar Gum) natural binders and derivatives such as alginates, chitosan, gelatin and gelatin derivatives, are also useful. Synthetic polymers such as polyvinylpyrrolidone (PVP), acrylic acid derivatives (Eudragit, Carbopol, etc.) and polyethylene glycol (PEG) are also useful as binders and matrix formers for the purpose of this invention. It may be useful to have these materials present in the range of from about 1.0 to about 60.0% (W/W)

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either in total, or individually in combination with one another. Preferably, these materials should be present in the range of from about 30 to about 50 percent (W/W).

It may also be necessary to incorporate a disintegrant into these pellets in order to facilitate dissolution of the active ingredient. For this purpose, any suitable tablet disintegrant can be utilized here, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol), cross-linked sodium carboxymethyl starch (Explotab, Primojel), cross-linked PVP (Plasdone XL) or any other material possessing tablet disintegrant properties.

For working examples of the first pellet see Examples 1 through 10 below.

The second pellet should have a sustained release profile, and needs to be able to address the changing pH of the GI tract, and its effect on the absorption of carbamazepine. This pellet should have all of the ingredients as mentioned for pellet A, as well as some organic acid which will be useful to reduce the pH of the microenvironment of the pellet, and thus facilitate dissolution. These materials are, but not limited to, citric acid, lactic acid, tartaric acid, or other suitable organic acids. These materials should be present in concentrations of from about 0 to about 15.0% (W/W), preferably these materials would be present in concentrations of from about 5.0 to about 10.0 percent (W/W). The process for manufacturing these pellets is consistent to the process described above for the previous pellet.

In addition to the pellet, this component should have a controlling coat applied to the surface of the pellet such that the release of the drug from the pellet is controlled and released over a 6-10 hour period. The materials used for this purpose can be, but are not limited to, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, nitrocellulose, carboxymethylcellulose, and any other cellulose ether, as well as copolymers of ethacrylic acid and methacrylic acid (Eudragit), or any other acrylic acid derivative (Carbopol, etc.) can be used. In addition, an enteric coating material can also be employed, either singularly, or in combination to the above non-pH sensitive coatings. These materials include, but are not limited to, hydroxypropylmethylcellulose phthalate and the phthalate esters of all the cellulose ethers. In addition, phthalate esters of the acrylic acid derivatives (Eudragit), or cellulose acetate phthalate. These coating materials can be employed in coating the surfaces in a range of from about 1.0% (W/W) to about 25% (W/W). Preferably these coating materials should be in a range of from about 8.0 to about 12.0 percent (W/W).

For working examples of the second pellet, see Examples 11 through 20 below.

The third pellet in this system should be qualitatively similar to the second pellet, in that the manufacturing process for producing this pellet is consistent with that of the first two pellets, and the microenvironment inside the pellet should be consistent with that of pellet B. However, this pellet should have some internal component breaking down in the pH of the lower GI tract. Thus, it will be necessary to include some enteric or pH sensitive material into the pellet to facilitate erosion and breakdown in the lower GI tract. This material can be, but is not limited to, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, any additional cellulose ether phthalates, any of the acrylic acid derivative phthalates (Eudragit), as well as any enteric coating material, such as shellac, zein, or others. The concentration of these materials in the pellet should be from about 1.0 to about 15.0% (W/W), preferably the concentration of materials should be from about 5.0 to about 10.0 percent (W/W).

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The coating of this third pellet should be similar to the coating for pellet B, except that it should have a considerable pH sensitivity associated with it. Therefore, it would be desirable to coat pellet C with any of the pH sensitive, or enteric coating materials listed above, either singularly, or in combination with any coating material mentioned above. This coating level of this pellet should range from about 1.0 to about 15.0% (W/W), preferably the concentration of materials should be from about 5.0 to about 12.0 percent (W/W).

For working examples of the third pellet, see Examples 21 through 28 below.

Each pellet should have its own dissolution profile associated with the formulation assigned to it.

BRIEF DESCRIPTION OF THE DRAWINGS

The target dissolution curves for the three units can be seen in FIG. 1. This figure shows a schematic of the three units, as well as the target dissolution for the materials. Depending on the formulation chosen in this invention, the exact ratios of each of the pellets may need to be adjusted. The amount of the first unit in the formulation should preferably range from about 5.0 to about 25.0%. The amount of the second unit in the dosage form should range from about 15.0 to about 90.0%. The dosage form for the third unit should be in a range of from about 5.0 to about 30.0%.

In accordance with another aspect of the present invention, there is provided a pharmaceutical composition in the form of robust pellets, in which carbamazepine is present in high loading. More particularly, the robust pellets contain the carbamazepine in an amount of at least sixty (60) percent, preferably seventy (70) percent or more, and most preferably eighty (80) percent or more by weight. The pellets are formed with a binder which is a pharmaceutically acceptable carrier which is comprised of an amphiphilic polymer having both hydrophobic and hydrophilic properties. The amphiphilic polymer preferably is also capable of forming both water in oil and oil in water emulsions; such a polymer would usually have both a hydrophobic and a hydrophilic portion. In general, such a polymer can be produced from a monomer having both a hydrophobic moiety and a hydrophilic moiety or by copolymerizing a hydrophobic monomer with a hydrophilic monomer.

In preparing the robust pellets, the amphiphilic polymer which is used as a binder or carrier in forming the robust pellets, is provided in the formulation prior to robust pellet formation. The formulation which includes the active, pharmaceutical, the hereinabove described amphiphilic polymer and any other ingredients to be included in formulating the robust pellets, is then granulated to produce solid robust pellets containing a high loading of carbamazepine. The pharmaceutically acceptable amphiphilic polymer used in the present invention may be comprised of solid amphiphilic polymer or a solution of amphiphilic polymer or a mixture of both depending upon the surface active properties of the amphiphilic polymer being used.

Although applicant does not intend to be bound to any theoretical reasoning, carbamazepine tends to be hydrophobic in nature and it is believed that amphiphilic polymers which have more hydrophobic tendencies (higher surface active properties) act as better binders for the high loading of carbamazepine. Therefore depending upon the specific amphiphilic polymer being used, and whether the polymer exhibits higher surface active properties as a solid or as a solution, will determine whether it is best to use a mixture of a solution of the amphiphilic polymer and solid

amphiphilic polymer in the robust pellet forming formulation; or whether it is best to use a solution of the amphiphilic polymer alone in the robust pellet forming formulation. The appropriate amphiphilic polymer formulation can then be granulated into robust pellets while still achieving a high loading of active insoluble pharmaceutical.

In some cases, it may also be possible to provide an amphiphilic polymer for use in the formulation by blending a polymer which does not include both a hydrophobic and a hydrophilic portion with a surfactant to thereby provide a polymer with surface activity.

When using a mixture of solid amphiphilic polymer and a solution of amphiphilic polymer in producing robust pellets, the present invention provides that the solution of the amphiphilic polymer make up no less than five percent (5%) by weight of the mixture of the solution of the amphiphilic polymer and the solid amphiphilic polymer. Preferably, the solution of the amphiphilic polymer is no more than seventy percent (70%) by weight of the total mixture of the solution of the amphiphilic polymer and the solid amphiphilic polymer. Most preferably, the solution of the amphiphilic polymer makes up from about forty percent (40%) by weight to about sixty (60%) by weight of the total mixture of the solution of the amphiphilic polymer and the solid amphiphilic polymer. In general, the polymer solution contains from 4% to 20%, by weight, of the polymer.

In another embodiment of the present invention, there is used a mixture of the amphiphilic polymer wherein the same amphiphilic polymer is to be used for both the solution and solid amphiphilic polymers. Additionally, the present invention also provides for two different amphiphilic polymers to be used for the solution and solid amphiphilic polymers.

The amphiphilic polymer used in the present invention may be any of a wide variety of pharmaceutically acceptable amphiphilic polymers. As representative examples thereof, there may be generally mentioned, all vinylpyrrolidone derivatives, all polyhydroxyls and all ethoxylated polymers that have surface-active properties. As representative of more specific examples there may be mentioned polyvinylpyrrolidone (PVP), PVP-VA copolymers (Kollidon VAG4), Poly-ether maleic anhydride, polyethylene glycol, polysorbates esterified celluloses, polyacrylates, polyvinylacetates or pluronics, for example, block copolymers of oxyethylene and oxypropylene.

In general most of pharmaceutically acceptable amphiphilic polymers, described above, should have a number average molecular weight of at least 5000 and preferably at least 50,000. In a preferred embodiment the amphiphilic polymer is polyvinylpyrrolidone, having a high number average molecular weight. High molecular weight polyvinylpyrrolidones are known in the art as having a molecular weight of at least 100,000. As representative of a polyvinylpyrrolidones having a high number average molecular weight there may be mentioned PVP K-90 which has a number average molecular weight of 360,000.

In addition to the amphiphilic polymer and carbamazepine, the pellets may include other materials used in the formation of pharmaceutical pellets. Representative examples of such ingredients may include but are not limited to pharmaceutically acceptable fillers, surface active agents, binders and disintegrants, specific examples of which are described below.

A preferred embodiment of the present invention provides that such robust pellets contain an amount of carbamazepine capable of maintaining the patient's blood concentration at from about 4 $\mu\text{g}/\text{ml}$ to about 12 $\mu\text{g}/\text{ml}$ over at least a 12 hour

time period, where the blood concentration of carbamazepine does not vary by more than 20%.

Another embodiment of the present invention provides for a composition for treating a patient comprising an effective amount of carbamazepine and a pharmaceutically acceptable carrier which are sufficient for maintaining a blood concentration of carbamazepine within the therapeutic range and as described above.

Using such dosage form it is preferred that the dose of carbamazepine administered each 24 hour period is from about 800 mg to about 1200 mg. The dose is adjusted by the administering physician based upon the age, sex and weight of the patient to maintain therapeutic blood levels of carbamazepine.

Since carbamazepine is needed to be absorbed into the bloodstream over at least a twelve-hour period, it is preferred that the drug be administered in a dosage form that will reliably remain in the GI tract, in a sufficiently high region as to favor absorption. To achieve and maintain the therapeutic range, a dose of from about 400 to about 600 mg per 12 hour period of carbamazepine this makes it necessary to have a high loading of drug in the pellets.

Another object of the present invention provides a method for producing robust pellets of carbamazepine which comprises blending a pellet forming formulation which includes a mixture of pharmaceutically acceptable amphiphilic polymer, and an carbamazepine, which is then granulated into robust pellets.

In a preferred embodiment of the present invention the pharmaceutical composition contains at least sixty percent (60%), preferably, seventy percent (70%) or more by weight of the carbamazepine. Most preferably, the present invention provides for a pharmaceutical composition which contains eighty percent (80%) or more of the carbamazepine by weight. As representative examples of such carbamazepine there may be mentioned the following: carbamazepine, ibuprofen, gemfibrozole, flutamide, estradiol, alprazolam, triazolam, lorazepam, and indomethacin.

The term W/W as used herein is representative of a weight to weight ratio of the material specified to the weight of the unit dosage form as a whole.

In accordance with a preferred embodiment of the present invention, there is provided robust pellets in which carbamazepine is present in high loading. In a particularly preferred embodiment there is produced three different types of pellets containing carbamazepine as the carbamazepine, one of which is an immediate release formulation, the second of which is a slow release formulation and the third of which is an pH-dependent formulation.

In general, the three different types of pellets are combined into a single dosage form for oral delivery. The immediate release formulation has a high loading of carbamazepine and may or may not be formed as a robust pellet formulation. However, the pellet is formed it must allow for the quick release of the carbamazepine. The slow release and pH-dependent formulation are formulated as robust pellets with a high loading of carbamazepine, most preferably, by using a high number average molecular weight polyvinylpyrrolidone having a number average molecular weight of at least 100,000, as the amphiphilic polymer (the carrier or binder) for forming the robust pellets. In producing the robust pellets the polyvinylpyrrolidone (PVP) is preferably provided in the formulation, prior to pellet formation, as a solution of PVP. Although having 100% of the amphiphilic polymer in solution is preferred, it may be possible to utilize a mixture of both solid polyvinylpyrrolidone (PVP) and a

solution of polyvinylpyrrolidone, wherein the solution of PVP is no less than fifty percent (50%) of the mixture, preferably no less than seventy percent (70%) of the mixture of solid PVP and solution of PVP. The PVP solution should contain from about 4% to about 20% by weight of the PVP.

In addition to the high loading of carbamazepine, the first unit is formulated with ingredients of a type generally employed in producing an immediate release dosage form. These materials can be, but are not limited to, microcrystalline cellulose (such as Avicel), corn starch, pregelatinized starch (such as Starch 1500 or National 1551), potato, starch, sodium carboxymethylated starch, sodium carboxymethylated cellulose, hydroxypropylmethyl cellulose, hydroxypropylcellulose, hydroxyethylcellulose, ethylcellulose, as well as any cellulose ether.

It may also be necessary to incorporate a disintegrant into this first unit in order to facilitate dissolution of the carbamazepine. For this purpose, any suitable tablet disintegrant can be utilized here, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol), cross-linked sodium carboxymethyl starch (Explotab, Primojel), cross-linked PVP (Plasdone XL) or any other material possessing tablet disintegrant properties.

In the second unit, in addition to the carbamazepine and PVP the unit is formulated with ingredients of a type generally employed in producing a sustained release dosage form. These ingredients need to be able to address the changing pH of the GI tract, and its effect on the absorption of carbamazepine. This pellet should have some organic acid which will be useful to reduce the pH of the microenvironment of the pellet, and thus facilitate dissolution. These materials are, but not limited to, citric acid, lactic acid, tartaric acid, or other suitable organic acids. These materials should be present in concentrations of from about 1 to about 15.0% (W/W), preferably these materials would be present in concentrations of from about 5.0 to about 10.0 percent (W/W). The process for manufacturing these units are consistent with the process-described above for the first unit.

In addition the second unit should have a controlling coat applied to the surface of the unit such that the release of the pharmaceutical from the unit is controlled and released over a 6-10 hour period. The materials used for this purpose can be, but are not limited to, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, nitrocellulose, carboxymethylcellulose, and any other cellulose ether, as well as copolymers of ethacrylic acid and methacrylic acid (Eudragit), or any other acrylic acid derivative (Carbopol, etc.) can be used. In addition, an enteric coating material can also be employed, either singularly, or in combination to the above non-pH sensitive coatings. These materials include, but are not limited to, hydroxypropylmethylcellulose phthalate and the phthalate esters of all the cellulose ethers. In addition, phthalate esters of the acrylic acid derivatives (Eudragit), or cellulose acetate phthalate. These coating materials can be employed in coating the surfaces in a range of from about 1.0% (W/W) to about 25% (W/W). Preferably these coating materials should be in a range of from about 10.0 to about 20.0 percent (W/W).

In addition to the carbamazepine and PVP the third unit is formulated with ingredients of a type generally employed in producing pH dependent release dosage form. These ingredients should be qualitatively similar to the second unit, in that both the manufacturing process, and the microenvironment inside the unit should be consistent with that of the second unit. However, this unit should have some internal component for breaking down in the pH of the lower GI tract. Thus, it will be necessary to include some enteric or pH sensitive material into the unit to facilitate erosion and breakdown in the lower GI tract. This material can be, but

is not limited to, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, any additional cellulose ether phthalates, any of the acrylic acid derivative phthalates (Eudragit), as well as any enteric coating material, such as shellac, zein, or others. The concentration of these materials in the unit should be from about 0 to about 15.0% (W/W), preferably the concentration of materials should be from about 0 to about 5 percent (W/W).

The coating of this third unit should be similar to the coating for the second unit, except that it should have a considerable pH sensitivity associated with it. Therefore, it would be desirable to coat the third unit with any of the pH sensitive, or enteric coating materials listed above, either singularly, or in combination with any coating material mentioned above. The coating level of this unit should range from about 1.0 to about 25.0% (W/W), preferably the concentration of materials should be from about 10.0 to about 20.0 percent (W/W).

For working examples of robust core pellet formulations, see Examples 29 through 34 below.

Each pellet should have its own dissolution profile associated with the formulation assigned to it. The target dissolution curves for the three units can be seen in FIG. 1. This figure shows a schematic of the three units, as well as the target dissolution for the materials. Depending on the formulation chosen in this invention, the exact ratios of each of the pellets may need to be adjusted. The amount of the first unit in the formulation should preferably range from about 5.0 to about 25.0%. The amount of the second unit in the dosage form should range from about 15.0 to about 70.0%. The dosage form for the third unit should be in a range of from about 5.0 to about 30.0%.

The formulation described above may for example be used in the treatment of epilepsy as well as other psychiatric, neurological and other disorders. With respect to such treatment, the amount of carbamazepine administered within the 3-unit formulation should be from about 800 mg to about 1200 mg over a 24 hour period. Preferably, carbamazepine is administered within the formulation is in an amount equal to from about 400 mg to 600 mg over a 24 hour period. The therapeutic blood dosage level of the patient being treated should not be less than 4 µg/ml and should not exceed 12 µg/ml of carbamazepine over at least a 12 hour time period. The dose would be adjusted by the administering physician based upon the age, sex and weight of the patient to maintain therapeutic blood dosage levels.

The following examples 1 through 29 are intended to further illustrate not to limit the present invention. The examples are representative of formulations for carbamazepine which do not require robust pellets but which are provided three groups, one for each pellet type as described above.

Pellet A: Immediate Release Component

	Percent	Kilograms
Example 1:		
Microcrystalline Cellulose, N.F. (MCC) (Avicel PH-101/102, Emccel, etc.)	40.0	0.4
Hydroxypropylmethylcellulose (HPMC) (Methocel E5/E50/K5/K50)	2.5	0.025
Croscarmellose, Type A, N.F. (Ac-Di-Sol)	2.0	0.02
Sodium Lauryl Sulfate (SLS)	0.1	0.001
Carbamazepine	55.4	0.554
Total	100.0	1.000

-continued

<u>Pellet A: Immediate Release Component</u>		
	Percent	Kilograms
<u>Example 2:</u>		
MCC	40.0	0.4
HPMC	5.0	0.05
Sodium Starch Glycolate, N.F. (Explotab, Primojel)	8.0	0.08
SLS	0.3	0.003
Carbamazepine	46.7	0.467
<u>Total</u>	100.0	1.000
<u>Example 3:</u>		
MCC	20.0	0.2
Pre-gelatinized Starch (STARCH 1500, National 1551)	15.0	0.15
Croscarmellose	5.0	0.05
Corn Starch, U.S.P. (as paste)	5.0	0.05
Diocetyl Sodiurn Sulfosuccinate (DDS)	0.5	0.005
Carbamazepine	54.5	0.545
<u>Total</u>	100.0	1.000
<u>Example 4:</u>		
MCC	15.0	0.15
MCC/Carboxymethyl Cellulose (CMC) (Avicel RC Grade)	15.0	0.15
Croscarmellose	5.0	0.05
SLS	0.5	0.005
Carbamazepine	64.5	0.645
<u>Total</u>	100.0	1.000
<u>Example 5:</u>		
MCC/CMC	20.0	0.2
Croscarmellose	3.0	0.03
Sodium Starch Glycolate	5.0	0.05
HPMC	8.0	0.08
DDS	0.5	0.005
Carbamazepine	63.5	0.635
<u>Total</u>	100.0	1.000
<u>Example 6:</u>		
MCC	10.0	0.10
MCC/CMC	10.0	0.10
Croscarmellose	5.0	0.05
DDS	0.5	0.005
Carbamazepine	74.5	0.745
<u>Total</u>	100.0	1.000
<u>Example 7:</u>		
MCC/CMC	25.0	0.25
Polyacrylic Acid (Carbomer)	10.0	0.1
SLS	0.2	0.002
Sodium Starch Glycolate	7.5	0.075
Carbamazepine	57.3	0.573
<u>Total</u>	100.0	1.000
<u>Example 8:</u>		
MCC	30.0	0.30
HPMC	7.5	0.075
Croscarmellose	5.0	0.05
Sodium bis-(2-ethylhexyl)sulfo- succinate (Aerosol OT)	1.5	0.015
Carbamazepine	56.0	0.560
<u>Total</u>	100.0	1.000
<u>Example 9:</u>		
MCC	25.0	0.25
HPMC	5.0	0.05
Mono/Di/Tri-glyceride Mixture (Atmul-84S)	10.0	0.1
SLS	0.5	0.005

-continued

<u>Pellet A: Immediate Release Component</u>		
	Percent	Kilograms
Carbamazepine	59.5	0.595
<u>Total</u>	100.0	1.000
<u>Example 10:</u>		
MCC	25.0	0.25
Polyvinylpyrrolidone (PVP) (Plasdone)	8.0	0.08
Sodium Monoglycerate (Myvaplex)	8.0	0.08
SLS	0.35	0.0035
Carbamazepine	58.65	0.5865
<u>Total</u>	100.00	1.0000
<u>Example 11:</u>		
MCC	30.0	0.3
HPMC	5.0	0.05
Sodium Monoglycerate	8.0	0.08
Tartaric Acid	5.0	0.05
SLS	0.2	0.002
Carbamazepine	51.8	0.518
<u>Total</u>	100.0	1.000
<u>Coating:</u>		
Ethacrylic/Methacrylic Acid Esters (Eudragit RS100)	45.0	0.45
Ethacrylic/Methacrylic Acid Esters (Eudragit RL100)	45.0	0.45
Propylene Glycol	9.0	0.09
Talc	1.0	0.01
<u>Total</u>	100.0	1.00
<u>Example 12:</u>		
Same core pellet as in example 11		
<u>Coating:</u>		
HPMC (Methocel E50)	45.0	0.45
Ethylcellulose (Ethocel)	45.0	0.45
Polyethylene Glycol 400 (PEG400)	10.0	0.10
<u>Total</u>	100.0	1.00
<u>Example 13:</u>		
Same core pellet as in example 11		
<u>Coating:</u>		
HPMC	20.0	0.20
Ethylcellulose	70.0	0.70
PEG400	10.0	0.10
<u>Total</u>	100.0	1.00
<u>Example 14:</u>		
MCC	15.0	0.15
MCC/CMC Mixture	15.0	0.15
Citric Acid	6.0	0.06
DSS	0.8	0.008
Carbamazepine	63.2	0.632
<u>Total</u>	100.0	1.000
<u>Coating:</u>		
HPMC (Methocel K5M)	10.0	0.10
HPMC (Methocel E50)	14.0	0.14
Ethylcellulose	66.0	0.66
PEG400	10.0	0.10
<u>Total</u>	100.0	1.00
<u>Example 15:</u>		
Core pellet from example 14		
Coating from example 11		

-continued

<u>Pellet A: Immediate Release Component</u>		
	Percent	Kilograms
<u>Example 16:</u>		
Core pellet from example 14		
Coating from example 12		
<u>Example 17:</u>		
Core pellet from example 14		
Coating from example 13		
<u>Example 18:</u>		
MCC	30.0	0.3
PVP	8.0	0.08
Mono/Di/Tri-Glyceride Mixture	8.0	0.08
SLS	0.3	0.003
Tartaric Acid	7.5	0.075
Carbamazepine	46.2	0.462
Total	100.0	1.000
<u>Coating:</u>		
Coating from example 11		
<u>Example 19:</u>		
Core pellet from example 18		
Coating from example 12		
<u>Example 20:</u>		
Core pellet from example 18		
Coating from example 13		
<u>Example 21:</u>		
Core pellet from example 18		
Coating from example 14		

<u>Pellet C: Delayed Release Component</u>		
	Percent	Kilograms
<u>Example 22:</u>		
<u>Core Pellet:</u>		
MCC	25.0	0.25
Hydroxypropylmethylcellulose Phthalate (HPMCP)	10.0	0.10
Tartaric Acid	10.0	0.10
Sodium Monoglycerate	7.5	0.075
DSS	0.5	0.005
Carbamazepine	47.0	0.470
Total	100.0	1.000
<u>Coating:</u>		
Cellulose Acetate Phthalate (CAP)	60.0	0.60
Ethylcellulose	25.0	0.25
PEG400	15.0	0.15
Total	100.0	1.00
<u>Example 23:</u>		
Core pellet from example 22		
<u>Coating:</u>		
Ethacrylic/Methacrylic Acid Esters (Eudragit line of enteric polymers)	85.0	0.85
Propylene Glycol	14.0	0.14
Talc	1.0	0.01
Total	100.0	1.00

-continued

<u>Pellet C: Delayed Release Component</u>		
	Percent	Kilograms
<u>Example 24:</u>		
Core pellet from example 22		
<u>Coating:</u>		
CAP	65.0	0.65
HPMCP	15.0	0.15
PEG 400	10.0	0.10
PEG 8000	10.0	0.10
Total	100.0	1.00
<u>Example 25:</u>		
<u>Core Pellet:</u>		
MCC	25.0	0.25
Mono/Di/Tri-glyceride Mixture	15.0	0.15
Tartaric Acid	10.0	0.10
CAP	10.0	0.10
DSS	0.8	0.008
Carbamazepine	39.2	0.392
Total	100.0	1.000
Coating as in example 22		
<u>Example 26:</u>		
Core pellet as in example 25		
Coating as in example 23		
<u>Example 27:</u>		
Core Pellet as in example 25		
Coating as in example 24		
<u>Example 28:</u>		
Core pellet as in example 25		
<u>Coating:</u>		
Shellac	85.0	0.85
Mineral Oil	13.0	0.13
SLS	0.5	0.005
Talc	1.5	0.015
Total	100.0	1.000
<u>Example 29:</u>		
Core pellet as in example 22		
Coating as in example 28		

The following Examples 30-35 represent robust core pellet formulations. The pellet should be made via a suitable process which makes the dosage form into a reasonably round unit. This process can be, for example, simple granulation, followed by sieving, extrusion and marumerization; roto granulation; or any agglomeration process which results in a pellet of reasonable size and robustness. To produce enteric or pH dependent or sustained release robust pellets one would need to coat these robust core pellets with the appropriate coating.

EXAMPLE 30

	% W/W	INGREDIENT	AMOUNT
60	80.00	Carbamazepine, USP	32.00 kg
	2.5	Microcrystalline Cellulose, NF (Avicel PH-101)	1.00 kg
	5.0	Lactose, NF (Hydrous, 310)	2.00 kg
	5.0	Tartaric Acid, USP (Anhydrous)	2.00 kg
	0.5	Sodium Lauryl Sulfate, NF	0.20 kg
65	5.0	PVP-VA Copolymer (Kolidon VAG4)	2.00 kg
	1.5	Talc, USP	0.60 kg

-continued

EXAMPLE 30

% W/W	INGREDIENT	AMOUNT
0.5	Polyethylene Glycol 400, NF	0.20 kg
*	Purified Water, USP	12.00 kg
100.00		40.00 kg

*Purified Water, USP is removed during processing.

EXAMPLE 31

% W/W	INGREDIENT	AMOUNT
80.00	Carbamazepine, USP	32.00 kg
2.5	Microcrystalline Cellulose, NF (Avicel PH-101)	1.00 g
5.0	Lactose, NF (Hydrous, 310)	2.00 kg
5.0	Citric Acid, USP (Anhydrous)	2.00 kg
0.5	Sodium Lauryl Sulfate, NF	0.20 kg
5.0	Povidone, USP (K-90)	2.00 kg
1.5	Talc, USP	0.60 kg
0.5	Polyethylene Glycol 400, NF	0.20 kg
*	Purified Water, USP	12.00 kg
100.00		40.00 kg

*Purified Water, USP is removed during processing.

EXAMPLE 32

% W/W	INGREDIENT	AMOUNT
80.00	Carbamazepine, USP	32.00 kg
5.0	Microcrystalline Cellulose, NF (Avicel PH-101)	2.00 kg
2.5	Lactose, NF (Hydrous, 310)	1.00 kg
5.0	Ascorbic Acid, USP (Anhydrous)	2.00 kg
0.5	Sodium Lauryl Sulfate, NF	0.20 kg
4.0	Polyethylene Glycol 8000	1.60 kg
1.0	Polyethylene Glycol 400	0.40 kg
1.5	Talc, USP	0.60 kg
*	Purified Water, USP	12.00 kg
100.00		40.00 kg

*Purified Water, USP is removed during processing.

EXAMPLE 33

% W/W	INGREDIENT	AMOUNT
80.00	Carbamazepine, USP (Screened)	32.00 kg
2.5	Microcrystalline Cellulose, NF (Avicel PH-101)	1.00 kg
5.0	Lactose, NF (Hydrous, 310)	2.00 kg
5.0	Tartaric Acid, USP (Anhydrous)	2.00 kg
0.5	Sodium Lauryl Sulfate, NF	0.20 kg
5.0	Polyether Maleic Anhydride	2.00 kg
0.5	Magnesium Stearate, USP	0.20 kg
1.0	Talc, USP	0.40 kg
0.5	Poloxamer 338	0.220 kg
*	Purified Water, USP	12.00 kg
100.00		40.00 kg

*Purified Water, USP is removed during processing.

EXAMPLE 34

% W/W	INGREDIENT	AMOUNT
80.00	Carbamazepine, USP	32.00 kg
2.5	Microcrystalline Cellulose, NF (Avicel PH-101)	1.00 kg
5.0	Lactose, NF (Hydrous, 310)	2.00 kg
5.0	Ascorbic Acid, USP	2.00 kg
0.1	Sodium Lauryl Sulfate, NF	0.04 kg
2.5	Polyoxamer 237, NF	1.00 kg
0.5	Polyoxamer 188, NF	1.00 kg
1.5	Talc, USP	0.60 kg
0.5	Polyethylene Glycol 400, NF	0.20 kg
*	Purified Water, USP	12.00 kg
100.00		40.00 kg

*Purified Water, USP is removed during processing.

EXAMPLE 35

% W/W	INGREDIENT	AMOUNT
80.00	Carbamazepine, USP	32.00 kg
2.5	Microcrystalline Cellulose, NF (Avicel PH-101)	1.00 kg
5.0	Lactose, NF (Hydrous, 310)	2.00 kg
5.0	Citric Acid, USP	2.00 kg
0.5	Sodium Lauryl Sulfate, NF	0.20 kg
5.0	Polyethylene Oxide, NF	2.00 kg
1.5	Talc, USP	0.60 kg
0.5	Glycerin, USP	0.20 kg
*	Purified Water, USP	12.00 kg
100.00		40.00 kg

*Purified Water, USP is removed during processing.

In addition, it is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described herein and that the invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

What is claimed is:

1. A pharmaceutical composition comprising a robust pellet containing carbamazepine, said pellet containing carbamazepine in an amount of at least seventy weight percent and including a binder containing a high number average molecular weight polyvinylpyrrolidone in an amount of about 5 wt. %.

2. A pharmaceutical composition comprising:

a sustained release robust pellet containing carbamazepine, said pellet containing carbamazepine in an amount of at least seventy weight percent and including a binder containing a high number average molecular weight polyvinylpyrrolidone in an amount of about 5 wt. %.

3. A pharmaceutical composition comprising:

an enteric release robust pellet containing carbamazepine, said pellet containing carbamazepine in an amount of at least seventy weight percent and including a binder containing a number average molecular weight polyvinylpyrrolidone in an amount of about 5 wt. %.

4. The composition of claim 1 wherein said polyvinylpyrrolidone has a number average molecular weight of at least 100,000.

5. The composition of claim 2 wherein said polyvinylpyrrolidone has a number average molecular weight of at least 100,000.

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6. The composition of claim 2 and further comprising a coating material, wherein said coating material is present in an amount of from about 1.0% (w/w) to about 25% (w/w).

7. The composition of claim 6 wherein said coating material is present in an amount of from about 10% (w/w) to about 20% (w/w).

8. The composition of claim 2 wherein said polyvinylpyrrolidone has a number average molecular weight of at least 100,000.

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9. The composition of claim 3 and further comprising a coating material, wherein said coating material is present in an amount of from about 1.0% (w/w) to about 25% (w/w).

10. The composition of claim 9 wherein said coating material is present in an amount of from about 10% (w/w) to about 20% (w/w).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,912,013
DATED : June 15, 1999
INVENTOR(S) : Edward M. Rudnic et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page.

Item [75], Inventor(s), delete “; **John McCarty**, Biscayne Park, Fla.; **Sandra Wassink**, Frederick; **Richard A. Couch**, Germantown, both of Md.”.

Signed and Sealed this

Eighteenth Day of March, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

PATENT CERTIFICATION

This NDA references in part data and information contained in NDA 20-712 (Carbatrol®). In accordance with 21 C.F.R. §§ 314.54 (v) and (vi), Shire Laboratories, Inc. hereby states that the Orange Book patents listed for the drug for which this application is submitted, namely, U.S. Patent No. 5,326,570 expiring July 23, 2011, and U.S. Patent No. 5,912,013 expiring June 15, 2016, are owned by applicant Shire Laboratories, Inc.

This NDA also references in part data and information contained in NDA 16-608 (Tegretol®). Accordingly, Shire Laboratories, Inc., pursuant to Section 505(b)(2)(A)(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)(2)(A)(i)), and FDA regulation 21 C.F.R. § 314.54(a)(1)(vi), provides a Patent Certification for this New Drug Application for Carbamazepine Extended Release Capsules, 100 mg, 200 mg and 300 mg, as follows:

Paragraph I Certification: Shire certifies that, in its opinion and to the best of its knowledge, no patent information for any unexpired patents has been submitted to FDA for the drug product covered by NDA 16-608.

**Appears This Way
On Original**

EXCLUSIVITY SUMMARY FOR NDA # 21-710

SUPPL # NA

Trade Name EQUETRO Generic Name carbamazepine

Applicant Name Shire HFD # 120

Approval Date If Known see signature page

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /X/ NO / /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /x/ NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /x/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

three (3)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /x/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
NOT APPLICABLE

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other

than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_x_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_x_/ NO /___/

If "no," state the basis for your conclusion that a clinical

trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /x/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /x/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /x/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SPD 105.301 _____

SPD 417.304 _____

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

___SPD 105.301 "NEW" _____

___SPD 417.304 "NEW" _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND #_59,050_ YES /_x_/ ! NO /___/ Explain: _____
!
!
Investigation #2 !
IND # _59,050 YES /_x_/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1	!		!
YES /___/ Explain _____	!	NO /___/ Explain _____	!
_____	!	_____	!
_____	!	_____	!
Investigation #2	!		!
YES /___/ Explain _____	!	NO /___/ Explain _____	!
_____	!	_____	!
_____	!	_____	!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x_/

If yes, explain:

See attached electronic signature page

Signature _____ Date _____

Title: _____

Signature of Office/ _____ Date _____
Division Director

Form OGD-011347 Revised 05/10/2004

cc:

Archival NDA

HFD- /Division File

HFD- /RPM

HFD-610/Mary Ann Holovac

HFD-104/PEDS/T.Crescenzi

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

12/9/04 02:52:42 PM

Dr. Katz' signature date is the approval date for this NDA.

Russell Katz

12/10/04 04:21:19 PM

MARKETING EXCLUSIVITY

Shire is claiming a three-year marketing exclusivity under 21 CFR 314.50(j) and 21 CFR 314.108(b)(4)(iv) for SPD417 for the treatment of acute, manic or mixed episodes associated with Bipolar I Disorders. This NDA application contains new clinical investigations (other than bioavailability studies) that are essential to the approval of this submission. These new clinical investigations were conducted by Shire, the applicant of this NDA. To the best of Shire's knowledge, these new clinical investigations meet the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).

The submission contains the results of 3 controlled clinical studies (SLI105.301, SLI105.302, and SPD417.304), and one long-term open label safety and efficacy (SLI105.303) along with references of all pharmacokinetic studies previously submitted in NDA 20-712. This clinical program was discussed and agreed with the Agency during a Type B meeting with the Division of Neuropharmacological Drug Products on 01 November 2001.

The following studies contained in this submission that are new clinical investigations as defined by 21 CFR 314.108(a) are:

- SLI105.301 – Phase 3
- SLI105.302 – Phase 3
- SLI105.303 – Phase 3
- SPD417.304 - Phase 3

These studies were conducted under IND 59,050.

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PEDIATRIC PAGE

NDA/BLA #: 21-710 Supplement Type (e.g. SE5): NA Supplement Number:

Stamp Date: 13FEB2004 Action Due Date: 13DEC2004

HFD 120 Trade and generic names/dosage form: EQUETRO (carbamazepine) extended release capsules, 100, 200, and 300 mg

Applicant: Shire Pharmaceuticals Therapeutic Class: antimanic

Indication(s) previously approved: As CARBATROL: epilepsy, trigeminal neuralgia

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1 (one)

Indication #1: acute manic or mixed episodes associated with Bipolar I Disorder

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min 0 kg _____ mo. _____ yr. Tanner Stage _____
Max 10 kg _____ mo. _____ yr. Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min 10 kg _____ mo. _____ yr. ✓ Tanner Stage _____
Max 17 kg _____ mo. _____ yr. ✓ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): January 30, 2009

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-710
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

12/9/04 02:54:46 PM

PREA information only cited here. Firm will be seeking
a written request in effort to obtain exclusivity
with their PREA study.

PEDIATRIC USE INFORMATION

In accordance with 21 CFR 314.55(b)(1)(a), and as agreed at the Type B Meeting of 01 November 2001, pediatric assessments are deferred. However, a pediatric plan will be submitted within 120 days of the date of final approval of the application, presuming ultimate approval of same.

Appears This Way
On Original

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Thursday, December 09, 2004 2:01 PM
To: 'Bates, Doris J'
Subject: RE: EQUETRO: LABELING REVISION REQUESTS: Package Insert

Dear Dr. Bates,

We agree to all the revisions listed below in the package insert and commit to include them in the final package insert.

Regards

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Thursday, December 09, 2004 12:10 PM
To: Lomri, Zohra; Bates, Doris J
Cc: Laughren, Thomas P; Katz, Russell G
Subject: RE: EQUETRO: LABELING REVISION REQUESTS: Package Insert

Dear Ms. Lomri:

I am attaching the most recent revision of the draft PI for EQUETRO.

Changes are as follows (you will see them in green in the text):

Page 2: Added a statement that the safety & effectiveness of EQUETRO is not established in pediatric and adolescent patients. (It is not yet approved in this indication for this population. The language here is standard.)

Page 3: appraised changed to apprised line 133

Page 5: lines 235-241. Removed several drugs not yet approved in the US and also the footnote pertaining exclusively to them.

Page 6: added felodipine, line 264.

Page 7: added pediatric use language and rounded the numbers off in table 3. One number has also been rounded in Table 4, page 8.

Again, as with the container labels, if you are in agreement with these changes, this can be confirmed by return e-mail; no revised copy of labeling need be prepared for us.

I will be available this afternoon as needed,

Doris J. Bates, Ph.D.

Regulatory Project Manager

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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**Appears This Way
On Original**

Bates, Doris J

From: Bates, Doris J
sent: Thursday, December 09, 2004 11:08 AM
To: 'Lomri, Zohra'
Cc: Bates, Doris J
Subject: RE: EQUETRO: LABELING REVISION REQUESTS

Good morning Ms. Lomri:

As per our telephone discussion (10:30 this morning), the Division has received and evaluated further recommendations from DMETS regarding your container labels as provided to us on Dec. 6. We urgently need your agreement to the following requests:

1. On the 120-capsule container labels, please include a usual dosage statement.
2. On the 120-capsule container labels, please relocate the statement "Should not be used with other carbamazepine containing products" so that it appears above the company's name, with increased prominence. As currently presented, this statement appears below the company name in a smaller font.
3. For the professional samples, please relocate the statement "Should not be used with other carbamazepine containing products" so that it appears above the statement "Patient samples - not for sale" and above the company's name, with increased prominence. As currently presented, this statement appears below the "Patient sample..." statement and next to the company's name.
4. For the professional samples, please relocate the "Rx only" statement to the principal display panel.
5. For the professional samples, please include a usual dosage statement.

You can confirm agreement via return e-mail, if there is no need for discussion of the above points. We do not need revised mock-ups; your written agreement will suffice. As also discussed this morning, there are further minor revisions to the package insert in progress, and I will send you the revised insert as soon as it is completed and cleared for transmission.

Best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, December 09, 2004 1:52 PM
To: 'Lomri, Zohra'; Mota, Linda
Cc: Bates, Doris J; Laughren, Thomas P; Katz, Russell G
Subject: RE: EQUETRO: LABELING REVISION REQUESTS

Good afternoon Ms. Lomri:

Yes, increasing the font size will suffice to increase the prominence of the statements in question. We accept the proposal to do so by either 1 or 2 points, depending on available space in the label.

We believe that your response, including this agreement regarding font size, constitutes agreement between Shire and the Division on final revisions to the container labels.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

-----Original Message-----

From: Lomri, Zohra [mailto:ZLomri@us.shire.com]
Sent: Thursday, December 09, 2004 1:28 PM
To: 'Bates, Doris J'; Mota, Linda
Subject: RE: EQUETRO: LABELING REVISION REQUESTS

Dear Dr. Bates, our responses are included below

Comment 1 :On the 120-capsule container labels, please include a usual dosage statement.

response: we will include the following statement on one of the side panels
"See package insert for dosage information"

Comment 2: On the 120-capsule container labels, please relocate the statement , with increased prominence. As currently presented, this statement appears below the company name in a smaller font.

Response: We agree to move the statement "Should not be used with other carbamazepine containing products" so that it appears above the company's name. We want clarification on the following: "with increased prominence" means increased font size. IF this is correct, we intend to increase by 1 or 2 point size based on the space available.

Comment 3: For the professional samples, please relocate the statement "Should not be used with other carbamazepine containing products" so that it appears above the statement "Patient samples - not for sale" and above the company's name, with increased prominence. As currently presented, this

statement appears below the "Patient sample..." statement and next to the company's name.

Response: we commit to move the statement "Should not be used with other carbamazepine containing products" so that it appears as recommended. Again, we want to confirm that increasing the font size is required and ensure that an increase of 1 or 2 point size is acceptable.

Comment 4: For the professional samples, please relocate the "Rx only" statement to the principal display panel.

Response: the Rx only will be moved to the right bottom corner of the main panel

Comment 5: For the professional samples, please include a usual dosage statement.

Response: we will include the following statement on one of the side panels "See package insert for dosage information".

Regards

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Thursday, December 09, 2004 11:08 AM
To: Lomri, Zohra
Cc: Bates, Doris J
Subject: RE: EQUETRO: LABELING REVISION REQUESTS

Good morning Ms. Lomri:

As per our telephone discussion (10:30 this morning), the Division has received and evaluated further recommendations from DMETS regarding your container labels as provided to us on Dec. 6. We urgently need your agreement to the following requests:

1. On the 120-capsule container labels, please include a usual dosage statement.
2. On the 120-capsule container labels, please relocate the statement "Should not be used with other carbamazepine containing products" so that it appears above the company's name, with increased prominence. As currently presented, this statement appears below the company name in a smaller font.
3. For the professional samples, please relocate the statement "Should not

be used with other carbamazepine containing products" so that it appears above the statement "Patient samples - not for sale" and above the company's name, with increased prominence. As currently presented, this statement appears below the "Patient sample..." statement and next to the company's name.

4. For the professional samples, please relocate the "Rx only" statement to the principal display panel.

5. For the professional samples, please include a usual dosage statement.

You can confirm agreement via return e-mail, if there is no need for discussion of the above points. We do not need revised mock-ups; your written agreement will suffice. As also discussed this morning, there are further minor revisions to the package insert in progress, and I will send you the revised insert as soon as it is completed and cleared for transmission.

Best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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12/9/04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-710	Efficacy Supplement Type - <i>not applicable</i>	Supplement Number <i>not applicable</i>
Drug: carbamazepine (Trademark: EQUETRO)		Applicant: Shire Pharmaceuticals
RPM: Bates	HFD-120	Phone # 301.594.2850
<p>Application Type: () 505(b)(1) (✓) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>(✓) Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p style="text-align: center;">Please see 505(b)(2) checklist</p>
❖ Application Classifications:		
• Review priority		(✓) Standard () Priority
• Chem class (NDAs only)		6 S (<i>new indication, previously approved chemical entity</i>)
• Other (e.g., orphan, OTC)		NONE
❖ User Fee Goal Dates		
		December 13, 2004
❖ Special programs (indicate all that apply)		
		(✓) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information		
• User Fee		(✓) Paid
• User Fee waiver		() Small business () Public health () Barrier-to-Innovation () Other (specify)
• User Fee exception		() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)
• Application Integrity Policy (AIP)		
• Applicant is on the AIP		() Yes (✓) No

<ul style="list-style-type: none"> This application is on the AIP 	() Yes (✓) No
<ul style="list-style-type: none"> Exception for review (Center Director's memo) OC clearance for approval 	NOT APPLICABLE
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(✓) Verified
❖ Patent	
<ul style="list-style-type: none"> Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(✓) Verified
<ul style="list-style-type: none"> Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	PLEASE SEE 505(b)(2) checklist 21 CFR 314.50(i)(1)(i)(A) () Verified 21 CFR 314.50(i)(1) () (ii) () (iii)
❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	PLEASE SEE EXCLUSIVITY CHECKLIST
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	See Previous Action Packages
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(✓) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	None. First cycle approval.
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(✓) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	(✓) Yes () Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(✓) Press Office will determine () None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	✓
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	✓
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	<i>See Tab Mc</i>
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	✓
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	<i>See approval letter</i>
<ul style="list-style-type: none"> Applicant proposed 	✓
<ul style="list-style-type: none"> Reviews 	✓ (DMETS: See Tab Mc)

❖ Post-marketing commitments	
• Agency request for post-marketing commitments	✓ See Approval Letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	✓ See Approval Letter
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting	✓
• Pre-NDA meeting	✓ (there were two)
• Pre-Approval Safety Conference	N/A, not an NCE
• Other	Filing Meeting
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	NOT APPLICABLE
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NOT APPLICABLE
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)	✓ (See Tabs J and K)
Clinical Information	
❖ Clinical review(s)	✓ (Tab L)
❖ Microbiology (efficacy) review(s)	Not Applicable
❖ Safety Update review(s)	Not Applicable
❖ Risk Management Plan review(s)	See Tab Mc
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	✓ (Tab G)
❖ Demographic Worksheet (NME approvals only)	Not Applicable
❖ Statistical review(s)	✓ (Tab N)
❖ Biopharmaceutical review(s)	✓ (Tab O)
❖ Controlled Substance Staff review(s) and recommendation for scheduling	Not Applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	✓ (Tab I)
• Bioequivalence studies	Not applicable
CMC Information	
❖ CMC review(s)	✓ (Tab Q)
❖ Environmental Assessment	
• Categorical Exclusion	✓
• Review & FONSI	
• Review & Environmental Impact Statement	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	Not applicable
❖ Facilities inspection (provide EER report)	Tab Q (✓) Acceptable () Withhold recommendation

❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Waived, See Tab Q
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	✓ (Tab P)
❖ Nonclinical inspection review summary	Not applicable
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	Not applicable
❖ CAC/ECAC report	Not applicable

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this page is the manifestation of the electronic signature.**

/s/

Doris Bates

12/9/04 02:56:41 PM

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, December 08, 2004 11:35 AM
To: Yasuda, Sally
Cc: Jackson, Andre J; Laughren, Thomas P; Bates, Doris J
Subject: RE: NDA 21710 - Shire's Response to FDA draft PI: with track changes on

This email confirms that I have spoken with the Shire representative, and confirmed all Phase 4 commitments (scope and timing) as they are reflected in the most recent draft of the approval letter. I have also confirmed that the Division will correct all of the labeling issues identified by Drs. Jackson and Yasuda, and the firm has accepted these corrections.

This email will be archived in DFS to document the firm's agreement with the phase 4 commitments identified and presented to date. The firm sent emails on December 6 and 7 agreeing in principle to these commitments, so the earlier dates will be shown in our approval letter unless additional commitments are generated (or these are modified) and further negotiation is required.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

-----Original Message-----

From: Yasuda, Sally
Sent: Wednesday, December 08, 2004 8:52 AM
To: Bates, Doris J
Cc: Jackson, Andre J; Laughren, Thomas P
Subject: RE: NDA 21710 - Shire's Response to FDA draft PI: with track changes on

There are a few errors in the Sponsor's document. In the "track changes document:

- 1) page. 5, paragraph 5 - the contraindication with nefazodone should remain in the label because nefazodone is available as a generic drug and this contraindication is consistent with nefazodone labeling.
- 2) page 6, paragraph 6: (regarding co-administration of carbamazepine and delavirdine) - delavirdine should not be capitalized.
- 3) page 7, drug interactions : "Agents that inhibits Cytochrome P450..." should read "Agents that inhibit Cytochrome P450..."
- 4) page 8 : Agents with Decreased Levels in the Presence of Carbamazepine due to Induction... - felodipine should be included (between felbamate and glucocorticoids) as indicated in OCPB version.

(Also in the titles of these sections - such as comment # 3 and #4 - the

words should be all capitalized or not - but they should do it consistently)

5) page 8 - footnote #6 - Agree with Sponsor that it is OK to delete this.

Sally

-----Original Message-----

From: Bates, Doris J
Sent: Monday, December 06, 2004 5:22 PM
To: Freed, Lois M; Fisher, J Edward; Jackson, Andre J; Yasuda, Sally
Subject: FW: NDA 21710 - Shire's Response to FDA draft PI: with track changes on
Importance: High

Hi everybody, this is the response from Shire to the labeling proposals. It looks to me, on first glance, as though they have accepted the changes from pharmtox and biopharm, but Tom L. and I would like you to see their response so that we can all be sure.

He'll follow up with you on this. Thanks, too, for your input on the draft action letter last week.

This has also been sent to the chemists for their input.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

-----Original Message-----

From: Lomri, Zohra [mailto:ZLomri@us.shire.com]
Sent: Monday, December 06, 2004 2:17 PM
To: Doris Bates (E-mail); Mota, Linda
Subject: NDA 21710 - draft PI with track changes on

Hello Doris, this is the package insert with all track changes on. My comments are in track changes and red and highlighted yellow. It is still too hard to understand, so a "cleaned" version will follow shortly.

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

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dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please reply to the sender confirming this, then delete the e-mail. We offer no guarantees that this email is free from any malicious code or other computer programs that may destroy and/or damage your computer software and/or hardware. <<track change PI from Shire Version 01 - 01 Dec 04.doc>>

Appears This Way
On Original

MEMO

To: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products, HFD-120

From: Linda M. Wisniewski, RN
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

Through: Denise P. Toyer, PharmD
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

Carol A. Holquist, RPh
Director, Division of Medication Errors and Technical Support, HFD-420

CC: Doris Bates, PhD.
Project Manager, Division of Neuropharmacological Drug Products, HFD-120

Date: December 7, 2004

Re: ODS Consult 04-0285-1 Equetro (Carbamazepine Extended-release Capsules, USP)
100 mg, 200 mg, and 300 mg; NDA# 21-710 (IND# 59, 050)

This memorandum is in response to a December 6, 2004 request from your Division for a review of the container labels and carton labeling for Equetro. A revised package insert labeling was not submitted for review and comment. The proposed proprietary name was found acceptable by DMETS on December 2, 2004 (See ODS Consult 04-0285).

DMETS reviewed the labels and labeling submitted December 6, 2004 from a safety perspective, and have identified the following areas of possible improvement, which might minimize potential user error. In addition, DMETS concurs with the changes noted in this submission except as discussed in section B1 below.

A. GENERAL COMMENT

The blue font on the contrasting blue background is difficult to read. Revise the color font of the proprietary name or the color of the background to a color that provides greater readability.

B. CONTAINER LABEL (120 capsules)

1. *Comment/Response B2:* The firm proposes changing the color to a light blue vs. a dark blue, DMETS notes that despite the different colors, the trade dress of this product makes the product virtually indistinguishable from Carbatrol. Of particular concern is when the two products would be stored alphabetically by established name. In this case, there would be two carbamazepine products next to each other with the same trade dress. This may contribute to

dispensing errors. Despite the different shades of blue, these two products could easily be confused. Revise the background of Equetro to a color other than blue so that it is easily distinguished from Carbatrol.



2. Include a usual dosage statement.
3. Relocate the statement 'Should not be used with other carbamazepine containing products' so that it appears above the sponsor's name with an increased prominence. As currently presented, the statement appears below the sponsor's name and in a smaller font.

C. CONTAINER LABEL (Professional Sample 14 and 30 count)

1. See GENERAL COMMENT.
2. Relocate the statement 'Should not be used with other carbamazepine containing products' so that it appears above the statement 'Patient samples – not for sale' statement and above the sponsor's name, with an increased prominence. As currently presented, the statement appears below the "patient sample..." statement and next to the sponsor's name.
3. The  graphic bisects the proprietary name, makes the proprietary name difficult to read, and detracts from its prominence. Delete this graphic.
4. The  background is very distracting and interferes with the readability of the proprietary name. Revise this to a less distracting presentation.
5. Relocate the 'RX Only' statement to the principle display panel.
6. Include a usual dosage statement.

D. INSERT LABELING

No insert labeling was provided at this time.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Linda Wisniewski
12/8/04 01:28:33 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/8/04 01:32:17 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/8/04 02:09:05 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: December 7, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Carbamazepine ER for the treatment of manic or mixed episodes in bipolar I disorder (monotherapy only)

TO: File NDA 21-710
[**Note:** This overview should be filed with the 2-13-04 original submission of this supplement.]

1.0 BACKGROUND

Carbatrol, the formulation of carbamazepine ER used in the clinical trials supporting this new indication, is currently approved and marketed for the treatment of epilepsy and trigeminal neuralgia (NDA 20-712). This NDA provides data in support of a new claim for a very similar formulation to Carbatrol as monotherapy for the short-term treatment of manic or mixed episodes in bipolar I disorder, in a dose range of 400 to 1600 mg/day.

It should be noted that, at the current time, there are 7 drugs specifically approved for the treatment of acute mania, i.e., lithium, Depakote (valproate), Zyprexa, Risperdal, Seroquel, Geodon, and Abilify. All of these except for lithium are approved only for short-term use in treating mania; lithium is approved for both acute treatment and for maintenance treatment of mania. Another drug, Lamictal, has also been approved for maintenance treatment in bipolar disorder, but not for acute treatment. Although not approved for treating mania, carbamazepine in various formulations has been in widespread clinical use for years in the treatment of both acute mania and for maintenance treatment in bipolar patients.

An IND 59,050 for studies supporting a claim for carbamazepine ER in mania was submitted 9-29-99, and all the sponsor's studies supporting this supplement were conducted under this IND. We had two communications with the sponsor regarding the development program for carbamazepine ER in the short-term treatment of mania:

-In an initial 11-1-01 preNDA meeting, we discussed the sponsor's program, i.e., 2 three-week monotherapy studies (301 and 302). We acknowledged that the application would likely be fileable if both studies were positive, and we discussed a number of issues pertinent to the format

and content of the supplement. We indicated that a longer-term trial would be expected as a phase 4 commitment, and that a pediatric program would ultimately be needed.

-In a second 11-13-04 preNDA meeting, it was acknowledged that study 302 had failed, but a third study, 304, was noted to be positive. Again, the focus was on a number of issues pertinent to the format and content of the supplement.

The proposal is to use essentially the same formulation as Carbatrol, but with a different capsule color and tradename for this expanded population. Thus, CMC data were submitted to support this slightly modified formulation, and these data were reviewed by Chhagan Tele, Ph.D. There was no need for a pharmacology review. Although no new drug interaction data were submitted as part of this NDA, OCPB did conduct a review of the extensive literature provided in support of drug interaction language in labeling, and provided advice on labeling language. The OCPB review was conducted by Andre Jackson, Ph.D. from OCPB. The primary review of the clinical efficacy and safety data was done by Robert Levin, M.D., from the clinical group. Ohidul Siddiqui, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The original NDA for this expanded indication was submitted 2-13-04, and the supplement was filed 3-31-04. There was no 4-month safety update.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

It is my understanding that all CMC issues regarding this new formulation of carbamazepine have been resolved. In addition, the proposed name, Equetro, has been accepted by DMETS.

3.0 PHARMACOLOGY

As the TBM carbamazepine ER is very similar to the marketed product, Carbatrol, except for a different capsule color, there were no pharmacology/toxicology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

No additional pk studies were conducted as part of this development program.

As noted, however, OCPB did conduct a review of the extensive literature provided in support of drug interaction language in labeling, and provided advice on labeling language. The OCPB review was conducted by Andre Jackson, Ph.D..

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review focused on results from 2 trials submitted in support of this supplement, i.e., 2 monotherapy trials (301 and 304), both of identical design. One other study, 302, was admittedly negative, and the sponsor was not basing any support for the claim on the results of this study. This study was identical in design to studies 301 and 304, except that it included patients who were non-responsive to lithium. We have not reviewed the efficacy results for this trial. Both 301 and 304 were 3-week, multicenter, randomized (1:1, carbamazepine ER:pbo), double-blind, placebo-controlled, flexible dose studies involving adult (≥ 18) bipolar I patients (DSM-IV) having manic or mixed episodes, with or without psychotic features. Patients must have been inpatients at the time of entry. Carbamazepine ER dosing was initiated at 400 mg/day, and was to be increased in increments of 200 mg/day to a maximum daily dose of 1600 mg/day, if tolerated. Dosing was on a bid basis. Lorazepam was permitted on a limited basis for control of agitation or insomnia. In both trials, the primary endpoint was change from baseline to final visit (LOCF) at the end of week 3 for the Young Mania Rating Scale (YMRS) total score, an 11-item scale including items related to both manic and psychotic behavior. The primary analysis was LOCF using ANCOVA on a modified ITT dataset, i.e., all randomized patients who received at least 1 dose of assigned treatment and who had baseline and at least 1 followup assessment. The statistical model included treatment group and center, and the baseline YMRS value as covariates.

5.1.2 Summary of Individual Studies

5.1.2.1 Summary of 301

This study was conducted at 24 sites in the US.

Patients were slightly more male than female (53:47), about 3/4 Caucasian, and the mean age was about 37. The mean carbamazepine ER dose after stabilization was about 952 mg/day. About 3/4 of both drug-treated and placebo-treated patients received concomitant lorazepam for the management of acute agitation; actual dosing data was not provided.

The intent-to-treat population was as follows:

-Carbamazepine ER	94
-Placebo	98

Proportions completing to 3 weeks were as follows:

-Carbamazepine ER 50/101 (50%)
-Placebo 46/103 (45%)

The results on the primary efficacy analysis are as follows:

Efficacy Results on YMRS Total Score for Study 301 (LOCF)

	Baseline MRS	Chng from BL MRS	[P-value(vs pbo)]
Carbamazepine ER (n=94)	27	-8	=0.033
Placebo (n=98)	27	-5	

The results also statistically favored drug in the OC analysis at weeks 1, 2, and 3.

Conclusion: Drs. Levin and Siddiqui considered this a positive study, and I agree.

5.1.2.2 Summary of 304

This study was conducted at 25 sites [19 in the US, and 6 in India].

Patients were more male than female (71:29), about 1/2 Caucasian, and the mean age was about 38. The mean carbamazepine ER dose after stabilization was about 726 mg/day. About ¾ of both drug-treated and placebo-treated patients received concomitant lorazepam for the management of acute agitation; actual dosing data was not provided.

The intent-to-treat population was as follows:

-Carbamazepine ER 120
-Placebo 115

Proportions completing to 3 weeks were as follows:

-Carbamazepine ER 80/122 (66%)
-Placebo 64/117 (55%)

The results on the primary efficacy analysis are as follows:

Efficacy Results on YMRS Total Score for Study 304 (LOCF)

	Baseline MRS	Chng from BL MRS	[P-value(vs pbo)]
Carbamazepine ER (n=120)	29	-15	<0.001
Placebo (n=115)	29	-7	

The results also statistically favored drug in the OC analysis only at week 3.

Conclusion: Drs. Levin and Siddiqui considered this a positive study, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Efficacy

Evidence Bearing on the Question of Dose/Response for Efficacy

There was no evidence provided in this application pertinent to the question of dose response for effectiveness.

Clinical Predictors of Response

Exploratory analyses were done, when feasible, to detect subgroup interactions on the basis of gender, age, and race. There was no clear indication of differences in response based on these covariates.

Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the YMRS total score observed in the positive studies was similar to that seen in other positive mania trials, and I consider this a sufficient effect to support an efficacy claim for this product in mania .

Duration of Treatment

No definitive data were presented in this supplement pertinent to the question of the longer-term efficacy of carbamazepine ER in mania.

5.1.4 Conclusions Regarding Efficacy Data

These 2 positive trials (both for monotherapy) support the claim for short-term efficacy of carbamazepine ER as monotherapy in the treatment of bipolar I patients with emergent manic or mixed episodes. The question of longer-term efficacy will have to be addressed in the future, as will the question of use in pediatric bipolar disorder.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data in the submission for carbamazepine ER in the treatment of mania were derived primarily from a total of n=299 carbamazepine ER-exposed patients in monotherapy studies (31.7 patient years). These data came from the 3 short-term monotherapy trials and also the 52-week open extension protocol. As noted, the carbamazepine ER doses ranged from 400 to 1600 mg/day. In addition, the sponsor provided an update for spontaneously reported adverse events. Finally, the sponsor included results from a literature review focusing on carbamazepine ER and bipolar disorder.

Overview of Safety Findings

Safety Profile in Clinical Trials:

Overall, the profile of adverse events, labs, vital sign, and ECGs observed in this relatively small sample of patients was not obviously different from that seen in the trials supporting other indications for carbamazepine ER. There were no new, unrecognized serious adverse events that could be reasonably considered related to carbamazepine ER use. There were no deaths. There were a number of SAEs among carbamazepine ER-exposed patients, but most were worsening of the underlying psychiatric condition, with no clear excess for drug vs placebo and, as noted, no new, unrecognized serious adverse events. All of the carbamazepine ER dropouts for likely drug-related adverse events were for events known to be associated with this drug. There was no signal for QTc prolongation. The profile of common and drug-related adverse events emerging from this database was as follows: dizziness, somnolence, ataxia, speech disorder, amblyopia, nausea, vomiting, dyspepsia, constipation, dry mouth, pruritis, and rash.

Although most detected laboratory changes were expected, there was also a signal for increased cholesterol and LDL concentrations. It may be useful to periodically monitor these during chronic treatment.

Other Sources of Safety Information:

Regarding postmarketing reports and reports from the published literature, there were no new, unrecognized serious adverse events that could be reasonably considered related to carbamazepine ER use.

Future Needs

While carbamazepine ER has been demonstrated to be reasonably safe in this population, as monotherapy, there is a need for systematic longer-term safety data in this population, given the likelihood that it will be used more chronically.

5.3 Clinical Sections of Labeling

We made a number of changes to the sponsor's proposed additions to labeling for this new formulation, and we have now reached agreement on final labeling for this product.

6.0 WORLD LITERATURE

As noted, the sponsor did provide a literature review, however, this did not reveal any signal of previously unrecognized SAEs.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, carbamazepine ER is not approved for the treatment of mania, either as monotherapy or as adjunctive therapy, in any countries.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 sites for this NDA: Lerman (Hoffman estates, IL) and Shiwach (Terrell, TX). Both sites were included in both studies 301 and 304. Although there were several minor deficiencies, overall, the data from these 2 sites were judged to be acceptable.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Shire has submitted sufficient data to support the conclusion that carbamazepine ER is effective and acceptably safe as monotherapy in the acute treatment of mania. We have also reached agreement on final labeling and phase 4 commitments, and I recommend that we issue the attached approval letter with our proposed labeling for this product.

cc:

Orig NDA 21-710 (Carbamazepine ER/Mania)

HFD-120/Division File

HFD-120/TLaughren/RKatz/RLevin/DBates

DOC: Memo_Carbamazepine ER_Mania_AP1.doc

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Laughren
12/7/04 08:14:01 AM
MEDICAL OFFICER

Bates, Doris J

From: Laughren, Thomas P
Sent: Tuesday, December 07, 2004 8:40 AM
To: Bates, Doris J
Cc: Laughren, Thomas P
Subject: RE: NDA 21-710: Current draft of AP letter
Doris,

The letter looks fine.

Thanks,

Tom

-----Original Message-----

From: Bates, Doris J
Sent: Monday, December 06, 2004 3:19 PM
To: Laughren, Thomas P
Subject: NDA 21-710: Current draft of AP letter

Tom, there are still some holes in this, of course, since we're waiting for DMETS to OK the labels that arrived today, and for Shire to get back to us on the Phase 4 proposals sent to them last week, and we've only just received their package insert counterproposal. However, the review team is OK with the letter re their respective areas. I got OKs from Biopharm, CMC, pharmtox, and Bob.

I'll have to ride herd on any revisions to the Phase 4s and any additional dates of conferences, agreements, etc. In the meantime, though, I thought you'd want to see this sooner rather than later, so here it is.

*Appears This Way
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Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Monday, December 06, 2004 12:52 PM
To: 'batesd@cder.fda.gov'; Mota, Linda
Subject: NDA 21-710 response to DMETS comments & revised bottle labels



Comment from Trade Label Sample Labels
ETS.doc (52 KB) DEC 04.pdf (23 KB) DEC 04.pdf (2

Hello Doris,

there are 3 attachments for your review. one addressing DMETS comments of Monday 29 November, a second attachment including revised trade bottle samples and the third attachment includes revised physician sample bottle labels.

As usual, a hard copy will be formally sent to your office by tomorrow.

The PI should follow shortly, I am working on finalizing the cleaned up version.

Kind regards

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

<<Comment from DMETS.doc>> <<Trade Label 06 DEC 04.pdf>> <<Sample Labels 06 DEC 04.pdf>>

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Comment:

The Agency has only the "[]" submitted Labeling at present. If you are able to commit to changing only the trademark and those items recommended below, we can continue the labeling review on that basis for now.

Response:

Shire commits to changing the trademark from "[]" to "EQUETRO™" in all the labeling. Regarding the items recommended below, our response is included for each separate comment. Please note there is no commercial Blister Packaging configuration for EQUETRO or Carbatrol®.

Finally, final draft label samples for the trade-dress and physician samples are included for your review.

A. General Comments

Comment A1:

1. The sponsor should propose additional information for patient and healthcare provider on their web site, www.carbatrol.com.

Response A1:

Shire commits to providing additional information for patient and healthcare provider on the website, www.carbatrol.com.

Comment A2:

2. Include the following statement to appear with prominence on container and blister labels, insert labeling and advertising of the product:

[

]

Response A2:

We acknowledge your comment and propose the following statement since it is more inclusive by highlighting all other carbamazepine containing drugs instead of focusing on just one drug. This is in line with the Risk Management Plan submitted in the briefing packet and dated 26 October 2004.

[

]

This statement will appear on all packaging containers, insert labeling and advertising of the product.

B. Container or Blister label {100 mg (14's and 120's), 200 mg (30's and 120's), 300 mg (30's and 300 mg (30's and 120's))

Comment B1:

relocate the expression of strength to immediately follow the established name on the principal display panel

Response B1:

Shire has relocated the expression of strength to immediately follow the established name on the principal display panel .

Comment B2:

DMETS notes that the Shire trade dress for container labels increases the look-alike properties between L J' and Carbatrol (see image below). In light of the potential for confusion between these products, DMETS encourages differentiation of trade dress.

Existing Carbatrol Label

Proposed L J Label

Response B2:

Shire acknowledges your comments and is proposing to change the color of the background from dark blue to light blue. This change combined to the other changes recommended (strength, bottle count) will result in a distinct trade look. Samples are included for your review.

Comment B3:

DMETS acknowledges comments from sponsor that L J will be available in the same strengths and dosage form as Carbatrol. Consideration should be given to making the L J capsule colors the same as the color of each Carbatrol strength.

Response B3:

After considering your proposal, Shire would like to keep the proposed capsule shell color in the NDA (yellow/opaque green, yellow/opaque blue, yellow/blue capsules). Shire believes the changes agreed upon for the look of the bottle labels trade-dress are sufficient to distinguish the two products and in keeping with the desire to keep both product distinguishable on the basis of the difference in dosing regimen.

Comment B4:

The 14 and 30 capsule container sizes appear to be a unit of use containers. Please assure that the closure for these package sizes complies with the "Poison Prevention Packaging" standard. We refer you to the CFR 1700.14 and 1700.15 for guidance.

Response B4:

The closure is child resistant and includes a heat seal induction seal, which is in compliance with the Poison Prevention Packaging standard.

Comment B5:

Relocate the net quantity of contents to appear at the top of the container label.

Response B5:

The net quantity of contents now appears at the top left corner of the main panel. As a result, the NDC number was moved to the top right corner of the main panel.

Comment B6t:

relocate the "Mfg By, Manufactured for " statement to appear on the side panel rather than the principal display panel.

Response B7:

The "Manufactured for " statement has been relocated to appear on the side panel rather than the principal display panel.

Comment B8:

1. *Decrease the prominence of the distributor name, "Shire", as it currently has the same prominence as the proprietary name.*

Response B8:

The prominence of the distributor name, "Shire", has been decreased and is now inferior to that of the proprietary name.

Comment B9:

2. *We encourage the use of consistency in the case (upper or lower case) for the established name.*

Response B9:

The established name is now consistently printed in lower case.

Comments from the CMC reviewer:

The CMC reviewer recommended adding the statement "protect from light" and revising the established name to read "(carbamazepine) extended-release capsules" instead of "(carbamazepine extended-release capsules)".

Response:

A statement "Protect from light" was added and the established name was revised to read "(carbamazepine) extended-release capsules". The word "(carbamazepine)" could not be moved to be next to "Equetro" as recommended by Dr. Tele due to space constrain, instead, it remains directly under "Equetro".

C. Insert labeling

Comment C1:

We note that container labels submitted for the package sizes, 100 mg (14's), 200mg (30's), and 300 mg (30's), are designated, "professional Samples". Unless the sponsor plans to market these packaging configurations, they should not appear in the HOW SUPPLIED section of package insert labeling.

Response C1:

The 100 mg (14's), 200mg (30's), and 300 mg (30's), are professional samples, not intended for sale. Therefore, they will be removed from the Package insert.

Comment C2:

Add a statement to the WARNING section, consistent with other dual trade name products such as Zyban/Wellbutrin. An examples statement from the WARNING section of Zyban labeling appears below.

Patients should be made aware that ZYBAN contains the same active ingredient found in WELLBUTRIN and WELLBUTRIN SR used to treat depression, and that ZYBAN

should not be used in combination with WELLBUTRIN, WELLBUTRIN SR, or any other medications that contain bupriopon.

Response C2:

Your comment is acknowledged. Shire has added the following statement to appear as the first paragraph of the **WARNING** section:

“Patient should be made aware that EQUETRO contains carbamazepine and should not be used in combination with any other medication that contains carbamazepine.”

The use of carbamazepine has been selected over that of CARBATROL® since it is more inclusive by highlighting all other carbamazepine containing drugs instead of focusing on just one drug. This is in line with the Risk Management Plan submitted in the briefing packet and dated 26 October 2004.

Appears This Way
On Original

6 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

12/6/04 02:25:05 PM

Courtesy copies sent extensively within DMETS. Please note that
the official copy of submission is not yet
in COMIS. An email reply can be sent
to 120 and I will take care of
the COMIS data entry for you once the
link is available. Many thanks!

Bates, Doris J

From: Bates, Doris J
Sent: Monday, December 06, 2004 2:37 PM
To: Beam, Sammie; Wisniewski, Linda; Toyer, Denise P; Hubbard, Lisa
Cc: Bates, Doris J; Katz, Russell G; Levin, Robert; Tran, Debi Nhu; Kang, Robert Robert
Subject: RE: N 021710 N 000 MR 20-Oct-2004 - Review

We have just received new labeling mockups from the firm by email. I have put them into DFS as a fresh consult since the firm did take into account comments from DMETS and has responded to those comments. That consult should arrive in DMETS shortly via DFS email.

Our action due date is COB next Monday, but we need to be ready to act by Friday afternoon this week. Since we appear to be going directly to approval on this application, if there are any problems with these labels that would make it inappropriate for them to be used at product launch, please let me know ASAP.

Otherwise, given the lateness of this new labeling information, please feel free to send a simple email with an overall recommendation if that is something you feel comfortable doing (i.e., if you think it is OK for these labels to be used at product launch). If you also wish to make specific recommendations for future revisions to the labels (and these revisions could be made post-approval), please feel free to provide those later, and 120 can provide comments to the firm when we receive their final labeling after the (presumed) approval action.

Many thanks, and much sympathetic support. I wish these things got sorted out a lot sooner, too. I'm doing all I can to help - the company was kind enough to provide these .pdf files at my request for you.

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

12/6/2004

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-420 (ODS/DMETS)

FROM: HFD-120 (Dr. Bates)

DATE December 6, 2004

IND NO.59,050

NDA NO. 21-710

TYPE OF DOCUMENT
new NDA submission –
new Proprietary name
labels

DATE OF DOCUMENT
Dec. 6, 2004 (sent online)

NAME OF DRUG
carbamazepine

PRIORITY CONSIDERATION

CLASSIFICATION OF
DRUG antimanic

DESIRED COMPLETION DATE:
Action due date December 13, 2004.
E-mail summary feedback OK.

NAME OF FIRM: Shire Pharmaceutical Development, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

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
 BIOAVAILABILITY 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:

See attached email and files received from firm on this date. Note firm has responded to DMETS recommendations regarding labeling and has attached mockups of container labels bearing the new trademark EQUETRO.

If the attached information is acceptable to DMETS, an e-mail indicating this will suffice for 120. Please feel free to contact Dr. Bates directly if there are any questions.

SIGNATURE OF REQUESTER see DFS signature

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Bates, Doris J

From: Bates, Doris J
Sent: Friday, December 03, 2004 4:00 PM
To: Oliver, Thomas F
Subject: RE: NDA 21-710 APletrdraft2DB with review team edits.doc

Tracking: Recipient Delivery
Oliver, Thomas F Delivered: 12/3/2004 4:00 PM

Hi Tom – Dr. Tele found one more needed change: the parentheses in the nonproprietary name. Here's how the text reads now:

We note your agreement to place only the nonproprietary drug name, carbamazepine, in parentheses, and to include the statement "Protect from light." in the storage instructions. These agreements will apply to the package insert and to all trade dress and physician sample bottle labels [FAXes from Shire to CMC review team, November 3 and November 8, 2004].

I've shifted the parens around in the letter wherever I used the nonproprietary name, so we should be OK.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

-----Original Message-----

From: Oliver, Thomas F
Sent: Friday, December 03, 2004 3:57 PM
To: Bates, Doris J
Subject: RE: NDA 21-710 APletrdraft2DB with review team edits.doc

Doris,

Have a nice weekend!!

Tom

-----Original Message-----

From: Bates, Doris J
Sent: Friday, December 03, 2004 3:34 PM
To: Oliver, Thomas F
Subject: RE: NDA 21-710 APletrdraft2DB with review team edits.doc

Great! We're set to go to Tom and Rusty now. Thanks heaps.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I

Center for Drug Evaluation and Research

-----Original Message-----

From: Oliver, Thomas F

Sent: Friday, December 03, 2004 3:16 PM

To: Bates, Doris J

Subject: RE: NDA 21-710 APletrdraft2DB with review team edits.doc

Doris,

The revised letter (i.e., removal of the second/third sentences regarding stability data) looks good.

Thanks,

Tom

-----Original Message-----

From: Bates, Doris J

Sent: Friday, December 03, 2004 2:46 PM

To: Oliver, Thomas F

Subject: NDA 21-710 APletrdraft2DB with review team edits.doc

Hi Tom, per our discussion here's the revised letter. I've gotten OKs from pharm/tox, clin, and OCPB. Let me know if these revisions take care of things for CMC,

thanks,

Doris

Bates, Doris J

From: Laughren, Thomas P
Sent: Thursday, December 02, 2004 4:07 PM
To: Bates, Doris J
Subject: RE: Mins Nov 9 discussion.doc

Doris,

Look ok to me.

Tom

-----Original Message-----

From: Bates, Doris J
Sent: Thursday, December 02, 2004 3:43 PM
To: Laughren, Thomas P; Oliver, Thomas F
Subject: Mins Nov 9 discussion.doc

Hello Tom & Tom:

I've also sent this to DMETS for their review and comment. I can sign for the attendees; feel free to send comments/changes.

Altho these are technically due on the 9th, our action is due on the 13th, so I don't think the firm will mind if we are a few days late, under the circs.

D.

Table of Contents
NDA 21-710
EQUETRO (carbamazepine)
100, 200, and 300 mg Extended-Release Capsules

Approval Package:

Volume 1 of 1

- A. Table of Contents
- B. Action Package Checklist (for AP action)
- C. Action Letter
 - Approval letter with labeling (clean)
- D. Labeling
 - Agreed-upon labeling for AP action (see Tab C)
 - Comparison of Agreed-upon AP labeling to current Carbatrol labeling
 - Current Carbatrol insert
 - Current Tegretol XR insert
 - Container / Carton Labeling
- E. Patent Information (505(b)(2)checklist, certification, exclusivity request from applicant)
- F. Exclusivity Checklist
- G. Pediatric Information
 - Pediatric Page
 - Inadequate PPSR Letter (to IND: Not Releasable Under FOI)
 - Partial deferral and partial waiver information (PREA)
- H. User Fee information and Debarment Certification
- I. DSI
 - ◆ Letter to Dr. Lerman
 - ◆ Letter to Dr. Shiwach
 - ◆ CIS
- J. Division Director Memo
- K. Clinical Team Leader Memo
- L. Clinical Review
- M. Safety Review (see clinical review)

Table of Contents
NDA 21-710
EQUETRO (carbamazepine)
100, 200, and 300 mg Extended-Release Capsules

Approval Package:

Volume 1 of 1

- Mc. Consult Reviews
 - Reviews of proposed trademarks
- N. Statistical Review
- O. Biopharmaceutics / Clinical Pharmacology Review
- P. Pharmacology Memo (Re Labeling)
- Q. Chemistry Review
- R. Correspondence
 - Applicant to FDA
 - FDA to Applicant
- S. Minutes of Meetings
 - Pre-Supplement Meeting November 1, 2001
 - Pre-NDA Meeting November 13, 2003
 - Filing Meeting March 31, 2004
 - Trademark Discussion Meeting November 9, 2004
- T. ISE (See Clinical Review)
- U. ISS (See Clinical Review)
- V. Submission History
 - Log of Documents Submitted to NDA (DSS and EDR versions)

Bates, Doris J

From: Toyer, Denise P
Sent: Thursday, December 02, 2004 11:33 AM
To: Bates, Doris J; Beam, Sammie; Wisniewski, Linda; Hubbard, Lisa
Cc: Mahmud, Alina; Hoppes, Charles V
Subject: RE: NDA 21-710 Draft AP letter

Doris,

We've looked over your draft Phase 4 commitments and do not have any additional comments. Thank you for allowing us the opportunity to review this comment.

Denise.

-----Original Message-----

From: Bates, Doris J
Sent: Thursday, December 02, 2004 10:53 AM
To: Beam, Sammie; Wisniewski, Linda; Hubbard, Lisa
Cc: Mahmud, Alina; Toyer, Denise P; Hoppes, Charles V
Subject: NDA 21-710 Draft AP letter

Hi folks

This is the draft AP letter for the carbamazepine mania NDA - please check the Phase 4 commitment I requested for educational materials concerning the fact that carbatrol and whatever-this-will-be both have carbamazepine in them.

I have to contact the firm, propose all the phase 4 commitments (except PREA, we just drop that on them) and get their written consent to both the commitments and the deadlines, before we can take the final action, so I do need to know if this is OK (including deadline). If you can get back to me by COB Friday that would be great, otherwise let me know if it's likely to be Monday next week. Many thanks again, and I'll send the new labeling mockups over the minute I see them.

Sincerely,

Doris

Bates, Doris J

From: Jackson, Andre J
Sent: Thursday, December 02, 2004 11:26 AM
To: Bates, Doris J
Subject: RE: NDA 21-710: Draft Approval Letter. Please see Message.
The dissolution information is correct.

-----Original Message-----

From: Bates, Doris J
Sent: Thursday, December 02, 2004 10:44 AM
To: Oliver, Thomas F; Freed, Lois M; Yasuda, Sally; Fisher, J Edward; Tele, Chhagan; Jackson, Andre J; Levin, Robert
Cc: Laughren, Thomas P
Subject: NDA 21-710: Draft Approval Letter. Please see Message.

Hi folks

This is a draft approval letter for the carbamazepine mania NDA. Please note the following:

- the dissolution specs and expiration date are in the letter. I'd appreciate a doublecheck on these, just to make sure I got the media, etc. right.
- I added a comment about the need for a "protect from light" statement on container labels and in the PI, per CMC review and Co. agreement. Please doublecheck this, especially the bit about whether or not they can change the statement via the Annual Report mechanism.

- Regarding Pediatric PREA Phase 4 commitments, I indicated that we need an efficacy study in ages 10-17, and that we don't need either pediatric PK or a juvenile animal tox study. Correct me if I am mistaken about these.

- Regarding other Phase 4 commitments, I indicated that we need an adult long term monotherapy study. My understanding is that we don't expect much adjunctive use here.
- I do have a question: Carbamazepine is apparently associated with acute renal failure in some patients, but we have nothing in labeling to address either renal or hepatic insufficiency - do we need anything, should we ask for Phase 4 studies in these areas? Say, and it shall be done, or not, prn.
- I also added a request for educational materials related to the fact that carbamazepine is in both Carbatrol and whatever-this-will-be. DMETS already has something, but it's sparse. I'll be sending this letter to them also, so they can let me know if they do need more, or if this request can come out.

Re labeling, I sent all the DMETS comments to the firm (since we're giving them an alternate trademark) and they have agreed to make the changes in container/blister labeling etc. as requested. They will be sending new mockups, and DMETS is alerted.

Finally, I need feedback on this by late tomorrow if possible, for two reasons - I need to get this on to Tom Laughren and then Rusty, and *I have to contact the firm in advance and get their written consent to the Phase 4 commitments, including the proposed deadlines.* I can't do that until I know what we want them to commit to. Many thanks!

D.

Appears This Way
On Original

Bates, Doris J

From: Fisher, J Edward

Sent: Thursday, December 02, 2004 11:16 AM

To: Bates, Doris J

Subject: RE: NDA 21-710: Draft Approval Letter. Please see Message.

Doris, here's our section of the label. The letter looks fine. Thanks.

- Ed

Appears This Way
On Original

Bates, Doris J

From: Levin, Robert
Sent: Thursday, December 02, 2004 10:50 AM
To: Bates, Doris J
Subject: RE: NDA 21-710: Draft Approval Letter. Please see Message.

Thanks Doris.
The letter looks fine.
I'll look into the safety concerns that you mentioned.

Bob

-----Original Message-----

From: Bates, Doris J
Sent: Thursday, December 02, 2004 10:44 AM
To: Oliver, Thomas F; Freed, Lois M; Yasuda, Sally; Fisher, J Edward; Tele, Chhagan; Jackson, Andre J; Levin, Robert
Cc: Laughren, Thomas P
Subject: NDA 21-710: Draft Approval Letter. Please see Message.

Hi folks

This is a draft approval letter for the carbamazepine mania NDA. Please note the following:

- the dissolution specs and expiration date are in the letter. I'd appreciate a doublecheck on these, just to make sure I got the media, etc. right.
- I added a comment about the need for a "protect from light" statement on container labels and in the PI, per CMC review and Co. agreement. Please doublecheck this, especially the bit about whether or not they can change the statement via the Annual Report mechanism.

- Regarding Pediatric PREA Phase 4 commitments, I indicated that we need an efficacy study in ages 10-17, and that we don't need either pediatric PK or a juvenile animal tox study. Correct me if I am mistaken about these.

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- I also added a request for educational materials related to the fact that carbamazepine is in both Carbatrol and whatever-this-will-be. DMETS already has something, but it's sparse. I'll be sending this letter to them also, so they can let me know if they do need more, or if this request can come out.

Re labeling, I sent all the DMETS comments to the firm (since we're giving them an alternate trademark) and they have agreed to make the changes in container/blister labeling etc. as requested. They will be sending new mockups, and DMETS is alerted.

Finally, I need feedback on this by late tomorrow if possible, for two reasons - I need to get this on to Tom Laughren and then Rusty, and *I have to contact the firm in advance and get their written consent to the Phase 4 commitments, including the proposed deadlines*. I can't do that until I know what we want them to commit to. Many thanks!

D.

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ANNOTATED LABELING FOR SPD417

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On Original*

46 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

MEMO OF FILING MEETING

MEETING DATE: March 31, 2004

BACKGROUND: Carbatrol (carbamazepine) [NDA 20-712] is a 505(b)(2) NDA referenced to Tegretol [NDA 16-608] and approved for the treatment of epilepsy and trigeminal neuralgia. IND 59,050, specifically for the bipolar indication, was submitted September 29, 1999.

Two pre-submission meetings were held, on November 1, 2001 and November 13, 2003. In 2001, the firm's intention was to submit an efficacy supplement for Carbatrol. By 2003, this was modified to plans to submit a complete NDA for an alternate trademark/alternate trade dress product.

ATTENDEES: Drs./Mmes./Messrs. Katz, Laughren, Baweja, Jin, Oliver, Andreason, Hare and the individuals listed below.

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Dr. R. Levin
Secondary Medical:	
Statistical:	Dr. O. Siddiqui
Pharmacology:	Dr. E. Fisher (literature submission only)
Statistical Pharmacology:	
Chemistry:	Dr. C. Tele
Environmental Assessment (if needed):	
Biopharmaceutical:	Dr. A. Jackson
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Dr. N. Khin
Regulatory Project Management:	Bates
Other Consults:	DMETS: Ms Toyer, Mr. Hoppes

Per reviewers, are all parts in English or English translation? YES NO
 If no, explain:

CLINICAL FILE REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY NA _____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE REFUSE TO FILE _____

BIOPHARMACEUTICS FILE REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION: Mixed media submission, primarily paper, datasets electronic.

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

- The application is unsuitable for filing.
- The application, on its face, appears to be sufficiently organized and indexed to be considered suitable for filing. English language translations of the untranslated information will be provided by the applicant.
- The application, despite some deficiencies, appears to be sufficiently repairable to be rendered suitable for filing prior to the 60 day filing deadline.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Consult review will be needed from ODS/DMETS for trademark proposal []
2. No Pediatric Written Request exists for this drug substance under any trademark. [Carbatrol labeling includes information on pediatric use for the epilepsy indication.]
3. There are extensive issues related to patent certification which will be included in the 74-day letter. Refer to this letter and the 505(b)(2) checklist, filed in DFS as a separate document, for details.
4. Post Meeting Note: The 74-day letter was issued on April 26, 2004. The English translations were provided on July 15, 2004.

Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

12/2/04 02:51:09 PM

12/2/04

NDA 21-710
Questions for 505(b)(2) Applications
Page 1

1. Does the application reference a listed drug (approved drug)? YES NO
Two listed drugs.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
Carbatrol, NDA 20-712
Tegretol, NDA 16-608

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

(a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES, both Carbatrol and Tegretol XR. Note this NDA does not reference Tegretol XR, but the IR form.

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

(b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES and NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)
Yes for Carbatrol. No for Tegretol XR. The IR form of Tegretol is cited.

If "Yes," skip to question 6. Otherwise, answer part (c).

(c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO
Tegretol is technically an alternative since its highest strength is different from Carbatrol.

So is Tegretol XR.

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

NDA 21-710
Questions for 505(b)(2) Applications
Page 2

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES & NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)
Yes for Tegretol, No for Tegretol XR.

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

Generic carbatrol IR forms are available but are less similar than Carbatrol and Tegretol XR.

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

New indication, bipolar mania. Carbatrol and Tegretol have been used for this indication off-label for some time.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

Not an exact duplicate of Carbatrol. Tradename and trade dress will differ.
Also, Carbatrol itself is 505(b)(2).

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

NDA 21-710
Questions for 505(b)(2) Applications
Page 3

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification) -- relevant for Tegretol. Shire is the patent holder for Carbatrol, so the issue is moot for that drug.

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

• Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference? YES NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES NO

NDA 21-710
Questions for 505(b)(2) Applications
Page 4

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO,
the proposed drug is the same as the listed drug except for color and branding.

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # 59,050 NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

12/2/04 03:01:34 PM

CSO

See also Memos to File re patent certification decision,
communicated to PM on Day 46 pre-PDUFA goal
date and to firm on Day 45. Status
quo accepted stet.



NOV 24 2004

Food and Drug Administration
Rockville MD 20857

Mark Lerman, M.D.
Alexian Brothers Behavioral Health Hospital
1650 Moon Lake Blvd.
Hoffman Estates, Illinois 60194

Dear Dr. Lerman:

Between June 14 and July 12, 2004, Mr. Kujtim Sadiku, representing the United States (U.S.) Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations:

Protocol 105.301 entitled "A Three-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Safety and Efficacy Study of Extended Release Carbamazepine in Patients with Bipolar Disorder"; and

Protocol 417.304 entitled "a Phase III, Three-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Safety and Efficacy Study of Extended Release Carbamazepine in Patients with Bipolar Disorder" of the investigational drug carbamazepine (Carbatrol), performed for Shire.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Sadiku presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your letter dated July 21, 2004, and wish to emphasize the following:

1. You did not adhere to the investigational plan (21 CFR 312.60).

Protocol 105.301

- a. The protocol specified lorazepam use up to 6 mg/day during the lead-in/screening period, and up to 4 mg/day during the first week of double-blind treatment was permitted, but excluded after the second week of double-blind treatment. Three subjects were given doses of lorazepam in excess of the permitted dose at specified visits:

Subject 002 and 005: lorazepam 2 mg/day (Week 3)
Subject 004: lorazepam up to 8 mg/day (Screen/Lead-In)

- b. According to the protocol, the medical history and physical examination must be conducted at the screening visit. For subject 016, it was stated in the source document that the subject initially refused the physical examination on 5/16/01. However, you signed off in the CRF that the subject met all eligibility criteria and this subject was randomized to receive the study medication on 5/16/01. The physical examination was performed 2 days after randomization on 5/18/01.
- c. The protocol required assessments were not performed at certain study visits. For example:
- (1) For 4 subjects (005, 010, 013 and 014), the physical examination at final study visit (Visit 5) was not performed.
 - (2) For subject 005, the laboratory tests including urine drug screen and serum HCG were not done at Visit 2.
 - (3) Part of vital sign measurements (e.g. blood pressure) were not done at certain study visits for 4 subjects (004, 006, 007 and 008).

Protocol 417.304

- d. For subject 010, you did not perform physical examination at final study visit (Visit 5) as required by the protocol.
2. You did not promptly report to the sponsor the adverse events experienced by the following subjects [21 CFR 312.64(b)].

Protocol 417.304

Subject 005: Constipation (Visit 3)
Subject 009: Headache (Visit 5)

3. You did not maintain adequate records of the disposition of the drug [21 CFR 312.62(a)].
- There were discrepancies between the pharmacy drug accountability logs and the patient charts for the quantity of double-blind study medication dispensed and returned for 13 subjects in protocol 105.301 and 6 subjects in protocol 417.304.

We note in your written response that you have instituted standard operating procedures to ensure that the violations noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

Page 3 – Mark Lerman, M.D.

As the clinical investigator, it is your general responsibility to conduct clinical studies according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of subjects under your care.

We appreciate the cooperation shown Investigator Sadiku during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,



Joseph Salewski
Deputy Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 4 – Mark Lerman, M.D.

FEI:

Field Classification: RTC

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response received and reviewed

4)OAI

Deficiencies noted:

inadequate drug accountability records (04)

failure to adhere to protocol (05)

failure to report ADRS (16)

cc:

HFA-224

HFD-120 Doc.Rm. NDA 21-710

HFD-120 Review Div.Dir. Katz

HFD-120 MO Levin

HFD-120 PM D. Bates

HFD-46 c/r/s GCP File #11261

HFD-46 MO Khin

HFR-CE650 DIB Berg

HFR-CE6520 BIMO Yuscus

HFR-CE600 Investigator Sadiku

GCF-1 Seth Ray

r/d:NK(9/8-9/04)

reviewed:JPS(11/23/04)

f/t:11/23/04

O:\NK\ Letters\Lerman.vairr.doc

DSI Reviewer Note to Rev. Div. Medical Officer

For protocol 105.301, 16 subjects were enrolled and 10 subjects completed the study. For protocol 417.304, 10 subjects were enrolled and 4 subjects completed the study.

Based on the information provided in the EIR, the FDA investigator verified the presence of signed informed consent for each subject. The FDA investigator compared the data recorded in the source documents with the data recorded in the CRF for all subjects enrolled in both studies. A Form FDA-483 was issued at the end of inspection.

Inspectional findings:

Protocol 105.301

The protocol specified lorazepam use up to 6 mg/day during the lead-in/screening period, and up to 4 mg/day during the first week of double-blind treatment was permitted, but excluded after the second week of double-blind treatment. Three subjects were given doses of lorazepam in excess of the permitted dose at specified visits:

- Subject 002 and 005: lorazepam 2 mg/day (Week 3)
- Subject 004: lorazepam up to 8 mg/day (Screen/Lead-In)

According to the protocol, medical history and physical examination be conducted at the screening visit. For subject 016, the physical examination was performed 2 days after the subject was randomized to receive the study medication.

The protocol required assessments were not performed at certain study visits. For example:

- For 4 subjects (005, 010, 013 and 014), the physical examination at final study visit (Visit 5) was not performed.
- For subject 005, the laboratory tests including urine drug screen and serum HCG were not done at Visit 2.
- Part of vital sign measurements (e.g. blood pressure) were not done at certain study visits for 4 subjects (004, 006, 007 and 008).

Protocol 417.304

For subject 010, the physical examination at final study visit (Visit 5), as required by the protocol, was not performed.

The site did not report the following adverse events experienced by two subjects during the study.

- Subject 005: Constipation (Visit 3)
- Subject 009: Headache (Visit 5)

There were discrepancies between the pharmacy drug accountability logs and the patient charts for the quantity of double-blind study medication dispensed and returned for 13 subjects in protocol 105.301 and 6 subjects in protocol 417.304.

The review division should note above findings of protocol violation, adverse event reporting and drug accountability issues. The review division should consider any impact of such findings on study data.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joseph Salewski
12/6/04 10:26:03 AM

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Monday, November 22, 2004 3:23 PM
To: Lomri, Zohra; Bates, Doris J; Levin, Robert; Mota, Linda
Subject: RE: NDA 21-710: Dr. Levin request of last week



Bipolar_AE.ZIP
(47 KB)

Good afternoon,

attached is the data presented in the format discussed with Dr. Levi and Shire's statistician, Li Shi. hard copy and CD will be sent through regular channel early next week. Feel free to contact me if you have problems opening the attachment or if you need further information.

Kind Regards

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Thursday, November 18, 2004 5:10 PM
To: jacksonan@cder.fda.gov
Cc: Doris Bates (E-mail)
Subject: SPD417 -dissolution procedure



disso001.PDF (552 KB)



disso001.PDF (659 KB)

Good evening,

attached are the dissolution procedures one is for the 100mg strength, the other for the 200mg and 300mg strengths. I apologize for any delay. A hard copy is also being sent as an amendment to the application. Feel free to contact me at your earliest convenience if you need clarification or additional information.

Kind regards

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

<<disso001.PDF>> <<disso001.PDF>>

28 Page(s) Withheld



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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS (HFD-120)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
FAX #'s (301) 594-2858/594-2859
TELECOPIER COVER SHEET

NOTE: THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone at (301) 594-2775 and return it to us at the above address by mail, Attn: (HFD-120). Thank you.

DATE: 11-29-04

TIME: 11:35 a.m.

PLEASE DELIVER THE FOLLOWING PAGE(S) TO:

Tobira Lemri

NDA

21-710

FAX # 484-595-8156

Labeling

(containers & blisters)

FROM:

Dr. E. Bates

comments

Total number of pages, including cover page: 3

If you do not receive all pages or have any problems with receiving, call (301) 594-2850.

MESSAGE: _____

11-29-04

Per telephone call: we have only the "[]" submitted labeling at present. If you are able to commit to changing only the trademark & those items recommended below, we can continue the labeling review on that basis for new - ~~Dr.~~

A. GENERAL COMMENTS

1. The sponsor should propose additional information for patient and healthcare provider on their web site, www.carbatrol.com.
2. Include the following statement to appear with prominence on container and blister labels, insert labeling, and advertising of the product:

c

1

B. CONTAINER or BLISTER LABEL [100 mg (14's and 120's), 200 mg (30's and 120's), and 300 mg (30's and 120's)]

1. Relocate the expression of strength to immediately follow the established name on the principal display panel.

2. DMETS notes that the Shire trade dress for container labels increases the look-alike properties between Carbatrol and Carbatrol (see images below). In light of the potential for confusion between these products, DMETS encourages differentiation of trade dress.

Existing Carbatrol Label

Proposed Carbatrol Label

3. DMETS acknowledges comments from the sponsor that Carbatrol will be available in the same strengths and dosage form as Carbatrol. Consideration should be given to making the Carbatrol capsule colors the same as the color of each Carbatrol strength.
4. The 14 and 30 capsule container sizes appear to be a unit of use containers. Please assure that the closure for these package sizes complies with the "Poison Prevention Packaging" standard. We refer you to the CFR 1700.14 and 1700.15 for guidance.
5. Relocate the net quantity of contents to appear at the top of the container label.
6. Relocate the "Mfg By, Manufactured for:" statement to appear on the side panel rather than the principal display panel.
7. Decrease the prominence of the distributor name, "Shire", as it currently has the same prominence as the proprietary name.
8. We encourage the use of consistency in the case (upper or lower case) for the established name.

C. INSERT LABELING

1. We note that container labels submitted for the package sizes, 100 mg (14's), 200 mg (30's), and 300 mg (30's), are designated, "Professional Samples". Unless the sponsor plans to market these packaging configurations, they should not appear in the HOW SUPPLIED section of package insert labeling.
2. Add a statement to the WARNING section, consistent with other dual tradename products such as Zyban/Wellbutrin. An example statement from the WARNING section of Zyban labeling appears below.

Patients should be made aware that ZYBAN contains the same active ingredient found in WELLBUTRIN and WELLBUTRIN SR used to treat depression, and that ZYBAN should not be used in combination with WELLBUTRIN, WELLBUTRIN SR, or any other medications that contain bupropion.

20 November 2003

Shire

Russell Katz, MD
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RECEIVED

NOV 21 2003

DDR-120 / CDER

Product name: SPD417 (carbamazepine extended-release capsules)
IND number: 59,050
Submission Type: General Correspondence: Meeting Minutes
(13 November 2003 Pre-NDA Meeting)
Serial Number: 075

DUPLICATE

Dear Dr. Katz:

075(6c)

Please find enclosed, in triplicate, a meeting summary from the Pre-NDA meeting held between Shire and the Division on 13 November 2003. The purpose of the meeting was to discuss the format and content of the New Drug Application in CTD format.

If you have any questions concerning this submission, feel free to contact me at your earliest convenience at (240) 453-6447.

Sincerely,



Zohra Lomri
Senior Manager
Regulatory Affairs

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION INVESTIGATIONAL NEW DRUG APPLICATION (IND) (TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)		Form Approved: OMB No. 0910-0014. Expiration Date: January 31, 2006 See OMB Statement on Reverse.
		NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).
1. NAME OF SPONSER Shire Laboratories Inc.	2. DATE OF SUBMISSION 11/20/03	
3. ADDRESS (Number, Street, City, State and Zip Code) 1801 Research Blvd. Suite 600 Rockville, MD 20850	4. TELEPHONE NUMBER (Include Area Code) 240-453-6447	
5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code) Carbamazepine; 5H-Diben[b,f]azepine-5-carboxamide	6. IND NUMBER (If previously assigned) 59,050	
7. INDICATION(S) (Covered by this submission) Treatment of Bipolar Disorder		
8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: <input type="checkbox"/> PHASE 1 <input type="checkbox"/> PHASE 2 <input checked="" type="checkbox"/> PHASE 3 <input type="checkbox"/> OTHER _____ <div style="text-align: right; font-size: small;">(Specify)</div>		
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION. NDA 20-712		
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.		SERIAL NUMBER _____ <u>0</u> <u>7</u> <u>5</u> _____
11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)		
<input type="checkbox"/> INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)		
<input type="checkbox"/> RESPONSE TO CLINICAL HOLD		
PROTOCOL AMENDMENT(S): <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> CHANGE IN PROTOCOL <input type="checkbox"/> NEW INVESTIGATOR <input type="checkbox"/> RESPONSE TO FDA REQUEST FOR INFORMATION <input type="checkbox"/> REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED	INFORMATION AMENDMENT(S): <input type="checkbox"/> CHEMISTRY/MICROBIOLOGY <input type="checkbox"/> PHARMACOLOGY/TOXICOLOGY <input type="checkbox"/> CLINICAL <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> OTHER _____	IND SAFETY REPORT(S): <input type="checkbox"/> INITIAL WRITTEN REPORT <input type="checkbox"/> FOLLOW-UP TO A WRITTEN REPORT <input checked="" type="checkbox"/> GENERAL CORRESPONDENCE <div style="text-align: right; font-size: x-small;">(Specify)</div>
CHECK ONLY IF APPLICABLE		
JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.		
<input type="checkbox"/> TREATMENT IND 21 CFR 312.35(b) <input type="checkbox"/> TREATMENT PROTOCOL 21 CFR 312.35(a) <input type="checkbox"/> CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)		
FOR FDA USE ONLY		
CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
	RECEIVED NOV 21 2003 DDR-120 / CDER	
		IND NUMBER ASSIGNED:

12.

CONTENTS OF APPLICATIONThis application contains the following items: *(Check all that apply)*

1. Form FDA 1571 [21 CFR 312.23(a)(1)]
2. Table of Contents [21 CFR 312.23(a)(2)]
3. Introductory statement [21 CFR 312.23(a)(3)]
4. General Investigational plan [21 CFR 312.23(a)(3)]
5. Investigator's brochure [21 CFR 312.23(a)(5)]
6. Protocol(s) [21 CFR 312.23(a)(6)]
- a. Study protocol(s) [21 CFR 312.23(a)(6)]
- b. Investigator data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- c. Facilities data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- d. Institutional Review Board data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
7. Chemistry, manufacturing, and control data [21 CFR 312.23(a)(7)]
- Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
8. Pharmacology and toxicology data [21 CFR 312.23(a)(8)]
9. Previous human experience [21 CFR 312.23(a)(9)]
10. Additional information [21 CFR 312.23(a)(10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? YES NOIF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? YES NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Simon Tulloch, MD
Senior Vice President
US R&D

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

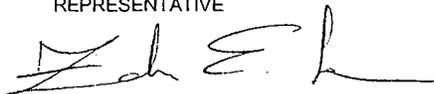
Alex Michaels, MD
Vice President, Medical Affairs

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Zohra Lomri
Senior Manager, Regulatory Affairs
U.S. Research and Development

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE



18. ADDRESS (Number, Street, City, State and Zip Code)

Shire Pharmaceutical Development Inc.
1801 Research Blvd. Suite 600
Rockville, MD 20850

19. TELEPHONE NUMBER (Include Area Code)

240-453-6447

20. DATE

11/20/03

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
ER (HFM-99)
.J1 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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Please **DO NOT RETURN** this application to this address.

Final Meeting Minutes – Issued 20 November 2003
Type B Meeting with FDA on 13 November 2003 (11:30 am – 12:30 pm)
NDA 21-710 – SPD417

FDA Attendees:

Russel Katz, M.D.	Director, Division of Neuropharmacological Drug Products
Doris Bates, Ph.D	Project Manager
Thomas Laughren, M.D.	Team Leader, Psychiatric Drugs Group
Earl Hearst, M.D.	Clinical Reviewer
Paul Andreason, M.D.	Team Leader, Psychiatric Drugs Group
Thomas Oliver, Ph.D.	Team Leader, CMC
Chhagan Tele, Ph.D.	CMC Reviewer
Raman Baweja, Ph.D.	Biopharmaceutics Team Leader

Shire Attendees:

Rick Lilley, Ph.D.	Senior Vice-President, Regulatory Affairs
Zohra Lomri, M.S.	Senior Manager, Regulatory Affairs
Alex Michaels, M.D.	Vice-President, Medical Affairs
Michael Pennick, B.Sc.	Manager, Preclinical Sciences
Robert Pullen, Ph.D	Vice President, Analytical Sciences
Sarah Sweeny	Manager, Clinical Programs
Susan Waring, M.S.	Sr. Manager Regulatory Operations
Yuxin Zhang, Ph.D.	Senior Director, Biostatistics

Summary of Agreements:

1. The sponsor will provide a proposal (i.e. algorithm) allowing the clinical reviewer to access all safety domains for each individual patient.
2. The sponsor will provide at the time of the filing an additional PDF file of the ISS, ISE, combined summary of the study reports, and each study report (with bookmarks and hyperlinks).
3. The sponsor will provide a combined summary of all study reports.
4. The sponsor will provide a combined list of all investigators and all study sites.
5. The sponsor will cross-reference the CMC section to the original NDA using the traditional NDA format.
6. A biowaiver will be granted to the sponsor.
7. Stability data requirements are waived if color change is [] within each strength. As a result, the sponsor will [] the color amount from the capsule shells within each strength (not across strength).]
8. The sponsor will provide dissolution data on capsules with new color(s).
9. The sponsor will include a description of the manufacturing process of the R&D batches manufactured to run dissolution testing.
10. The sponsor will include the most recent specifications for the active pharmaceutical ingredient (API).

11. The sponsor will provide the CMC reviewer with a qualitative and quantitative composition statement on the colors of the capsule shells for each strength prior to filing to get the CMC reviewer's concurrence.
12. 4-month safety update requirements are waived, as there are no ongoing trials.
13. The sponsor will provide a rationale in the filing for trade name selection along with the research steps leading to the selection of the proposed name.

Discussion:

Z. Lomri stated that the SPD417 capsules were Carbatrol pellets in capsule shells of a different color. The capsule shell new colors are obtained [] in the Carbatrol capsule shells.

Application Format

DR. Katz confirmed a CTD format was acceptable for this submission however the clinical team had requests.

The clinical team proceeded explaining they preferred accessing all safety domains (Lab tables, EKG, Vital signs and other) for each patient individually rather than having to go in each domain to gather this information for each patient. This process is cumbersome to them as they don't have SAS programs (only JUMP). The clinical team expects from the sponsor a proposal to comply with their request and wish to see/discuss it if necessary, prior to filing.

The CMC review team prefers the CMC section of the application to be presented in the traditional NDA format to ease cross-referencing during the review.

Trade Name

Dr. Katz clarified the Agency could not prevent the sponsor from proposing a different trade name but was strongly discouraging it and emphasized the Agency will try to prevent it to the extent permitted. He acknowledged FDA has approved different trade name for the same product but has always, immediately regretted it. FDA was urging the sponsor to reconsider having a different name for the product. The sponsor rationalized its decision to go for a separate trade name by the fact that the epileptic and bipolar patients represented very distinct groups, hence the need for a separate trade dress with distinct trade names. The sponsor added that if the name remained the same there was probably no value in having different colors for Carbatrol and SPD417 drug products. Dr. Katz agreed and added the sponsor may want to reconsider having different trade dresses altogether and emphasized the Agency's concern was a safety concern and wished they could prohibit the use of a different name for the same drug product (i.e. a patient could overdose on carbamazepine if prescribed Carbatrol by one physician and SPD417 by another).

Dr. Bates requested from the sponsor inclusion in the NDA of a rationale for why the sponsor needed a new trade name along with research process of the trade name. The sponsor agreed to provide the required information in the application.

Chemistry Manufacturing and Controls

Z. Lomri presented a slide showing quantitative and qualitative composition of the pellets (immediate-release, sustained-release and enteric-release) and the overall capsule fill of all strength (attachment). Post-meeting: Dr. Tele requested that Shire update the filing to identify the appropriate [] material name and "Type" as described in the current USP/NF.

In answer to Shire's request to create [] for Carbatrol and SPD 417, Dr. Katz stated that this option was impractical from FDA stand-point and recommended submitting CMC documentation to one application and cross-referencing to the other for future filings.

The CMC team leader requested the most current active ingredient specifications to be included in the filing. He confirmed with the sponsor that the packaging configuration of the drug product was identical to that of Carbatrol Drug Product for all three strengths.

CMC clarified waiving stability requirements on the condition that color change was achieved [] color(s) in each strength. Modifying colors by switching among strength would require submission of stability data in the application. The sponsor rationalized its proposal for [] of each coloring agent in the Carbatrol as the upper limit for coloring agent across strength on the basis that all the pellets were the same for all strengths, therefore stability data on one strength could apply to the other strengths. Dr. Oliver and Dr. Baweja agreed and added that for the same reason, a biowaiver was granted, however possible interaction of iso compound with the new color ratio across strengths could alter the dissolution profile of the drug product. Therefore, FDA was requesting dissolution data on the 3 proposed strength to be included in the application. Dr. Lilley indicated Shire had not planned to perform this testing prior to the filing, would the FDA accept submission of the dissolution data as an amendment to the application. Dr. Katz explained that this meeting was conducted to ensure inclusion of critical information in this application and that in his view and the CMC/Biopharm team view this data was critical.

The Biopharm team leader added that dissolution data collected using the currently approved dissolution method was acceptable and expected at the time of the NDA submission.

The CMC team leader suggested the sponsor submit for comment its final color selection specifications of the capsule shells to confirm acceptability of proposal prior to the NDA submission. He added a teleconference could easily be conducted for quick resolution as soon as the sponsor had finalized its specifications.

Dr. Pullen asked Dr. Oliver (CMC team leader) and Dr. Baweja (Biopharmaceutics team leader) [] in R&D facilities were acceptable to fulfill the dissolution requirements. They both agreed with Dr. Pullen and added a description of the manufacturing process of these R&D batches needed to be included in the NDA submission.

Clinical

The clinical team requested that additional electronic copies of ISS, ISE and final study report be provided in PDF file with bookmarks and hyperlinks. The team also requested for a truly integrated summary of all study reports along with a combined list of all investigators and all sites.

FDA expect analysis of post marketing data (from Carbatrol) along with SPD417 safety data analysis

The sponsor requested a waiver of the 4-month safety update since all studies were completed and no additional data was expected. FDA agreed.

Preclinical

Dr, Katz enquired on the accuracy and content of the drug-drug interaction package. M. Pennick confirmed a drug-drug interaction report from open literature studies would be included in the NDA. M. Pennick also confirmed the report included the most commonly used drugs for the treatment of bipolar symptoms. Dr Katz asked if the report contained individual patient data also on Lithium for example. Dr Michaels responded that no individual patient data was available in the literature however, the published literature reports mentioned carbamazepine plasma level in conjunction with Lithium. Dr. Katz stated that FDA will review the open literature based drug-drug interaction and emphasized that because it was in the literature it did not necessarily have any value.

Biopharmaceutics

Dr. Baweja, agreed that a biowaiver was acceptable but insisted on the necessity of dissolution data in the application (see discussion on CMC section)

Dr. Baweja also requested that a comprehensive and adequate labeling be provided.

Administrative

Dr. Bates asked Z. Lomri to ensure an environmental assessment was included as well as a pediatric waiver request, alternatively a pediatric study plan could be provided.

MINUTES OF MEETING WITH FIRM
SPD 417 (Carbamazepine Controlled-Release Capsules)
(Acute Mania, Bipolar Disorder), IND 59,050
Shire Pharmaceutical Development Inc.
Type B (Pre-NDA) Meeting

DATE: November 13, 2003

LOCATION: WOC II Rm. 4034

PARTICIPANTS: *Shire:* R. Lilley, Z. Lomri, A. Michaels, M. Pennick, R. Pullen, S. Sweeny, S. Waring, Y. Zhang

FDA: R. Katz, T. Laughren, P. Andreason, E. Hearst, R. Baweja, T. Oliver, C. Tele, D. Bates

Background: Shire holds two INDs and one approved NDA for carbamazepine in HFD-120.

Application	Number	Active Since	Indication
IND	38,793	January 31, 1992	Epilepsy
IND	59,050	September 30, 1999	bipolar disorder (acute mania)
NDA	20,712	September 30, 1997 (Approved)	Epilepsy

Shire initially planned to submit a supplemental NDA (2001 – 2002) for Carbatrol in treatment of acute mania associated with bipolar disorder (see meeting minutes, Nov. 1, 2001). In August 2003, the firm indicated intent to submit a separate NDA for a product based on the current approved Carbatrol, with an alternate trademark and trade dress. A briefing book was submitted on Oct. 13, 2003 (N074).

Discussion: The course of discussion followed the sequence of questions as presented in the briefing book (paraphrased below; includes details added in meeting).

1. The firm proposes to submit a paper application in CTD format, with the exception of electronic Case report forms and Case report tabulations (CRFs, CRTs). Efficacy and safety data will be provided as SAS transport files. Electronic portions will follow the E-NDA format.
 - FDA also requested that the ISS, ISE, and final study report be provided in e-format (.pdf), bookmarked and hyperlinked, if possible.
 - FDA agreed that no 120-day safety update would be needed; no trials are ongoing. However, postmarketing safety data should be provided for Carbatrol, with an attempt to separate out patients identified as bipolar, or those taking coadministered mood stabilizing drugs.
 - Dr. Laughren explained the need for information to be organized so that the reviewer can quickly access individual patient safety information such as EKGs, lab results, etc., in a time-by-variable display for each patient, i.e., patient profiles.
 - Shire will submit a proposal for patient profile information following the meeting, prior to submission, for FDA feedback.
2. Shire proposes to cross reference the CMC Module (Module 3) to the existing approved NDA, but to submit information on the manufacturing, testing, and packaging sites, plus a detailed description of the proposed trade dress.
 - Shire presented a slide showing the qualitative and quantitative composition of SPD 417 vs. Carbatrol for each capsule strength (Attachment 1).
 - The CMC review team requested that the CMC information be provided in NDA format at this time to make cross-referencing as direct as possible. Otherwise, relevant cross references are acceptable.

- NOTE: stability data requirements are waived, provided the color change for the SPD capsules is [] colorants within each strength vs. the Carbatrol formulation. This waiver cannot be applied if colorant compositions change across strengths rather than *within*.
 - NOTE: Shire will include the most current specifications for carbamazepine (drug substance) in the submission, along with specifications for the dosage forms.
 - The Biopharm review team requested comparative dissolution data for each strength of SPD 417, vs. each strength of Carbatrol, from batches manufactured using production type equipment. Profiles should be generated using the currently approved method and specifications for Carbatrol capsules. The manufacturing process for the exhibit batches should be included in the original submission (proposed commercial process will be cross-referenced). NOTE: granting of a waiver from bioequivalence requirements is based on the assumption that these data will be provided (as amended below post-meeting).
 - Shire proposed [post meeting] to submit data for the 100 mg SPD capsule using [] batches because of [] This proposal was accepted by FDA provided (a) comparative dissolution data are submitted for the [] batches as part of the original submission and (b) the NDA is promptly amended with data for [] batches, including comparative dissolution data. [Shire proposes to amend the NDA within 30 days of its submission.]
 - The Biopharm team also requested that literature information on drug-drug interactions be accompanied, wherever possible, by the individual data on which the relevant publications are based, if these data can be obtained from the investigators. The ultimate acceptability of literature data as sufficient, in this area, will be a matter for review.
 - The Biopharm team additionally requested that the labeling submitted for the SPD 417 product include appropriate text relevant to the submitted drug-drug interaction information (literature and/or data).
3. Shire proposes [] by both the Carbatrol trademarked product (N 20712) and the new product (currently designated SPD417).
- FDA explained the impracticality of accessing information in this format and requested that it be included directly in one NDA and cross-referenced in future applications where relevant.
4. Shire requests FDA suggestions for optimizing the presentation of data in the application.
- FDA requested additional information in e-format (point 1. above)
 - FDA noted the need for an Environmental Assessment section or categorical exclusion claim, and for appropriate pediatric information, in the initial submission.
5. Shire requests FDA feedback regarding the adequacy of the proposed package for CMC (stability) and OCPB (bioequivalence)
- See above discussion for these points.
 - TRADEMARK: FDA explained that current policy does not forbid submission of alternate trademarks, but the Agency still prefers to discourage it. Shire explained that their interest in pursuing this option arises from the differing patient populations.
 - FDA noted that the risk of overdose can be increased by the use of different trademarks (patients unwittingly taking both trademarked versions of the same drug).
 - FDA advised Shire that a different trademark proposal requires a different trade dress as well, and that conversely, a different trade dress requires a different trademark. If a different trademark is not adopted, a different trade dress cannot be used.

Shire Pre-NDA Meeting, November 13, 2003

- On this basis the FDA again questioned the basis for submitting a distinct trademarked product.
- Following the meeting Shire was advised that if they do still wish to submit an alternate trademarked product, they should include any information available on tests they have performed re the potential for tradename confusion, as well as a rationale to support the proposal for use of an alternate tradename, in the initial submission.

Post Meeting Notes:

- The anticipated submission date for NDA 21-710 (preassigned number) is end January, 2004.
- Shire is providing information on the capsule shell composition and will provide physical samples for color comparison (proposed SPD 417 shells and current Carbatrol shells).
- Shire is preparing [] the marketed Carbatrol product. A proposal for this [] in the dissolution specification, with anticipated timelines, was provided by the firm following the meeting (Attachment 2).

*Please see electronic signature page.
Electronic signatures appear on last page of document,
Following attachments.*

Doris J. Bates, Ph.D.
Regulatory Project Manager

Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drugs Group

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates
12/12/03 03:00:40 PM

Thomas Laughren
12/12/03 03:03:04 PM

Russell Katz
12/12/03 03:25:13 PM

NDA 21-710
Carbamazepine in Acute Manic/Mixed Episodes (Bipolar I Disorder)
Meeting with Firm re Trademark Issues
November 9, 2004: 4:30 P.M., HFD-120 Conference Room

Participants: **FDA:** Drs./Messrs./Mmes. Temple (premeeting only), Katz, Laughren, Oliver, Mahmud, Hoppes, Toyer, Bates

Shire: Drs./Messrs./Mmes Lewis, Lomri, Rasmussen, Salinas, Tulloch, Widmer

Background. NDA 21-710, submitted and received February 13, 2004, is an application for the use of carbamazepine extended-release capsules in the treatment of acute manic/mixed episodes associated with bipolar I disorder. The NDA is held by Shire. The product is the same as the approved drug product Carbatrol, in terms of dosage form and dosage strength, but is intended for marketing under a different proprietary name and with a different trade dress (capsule colors, branding).

Carbatrol is approved for the treatment of epilepsy and trigeminal neuralgia, but has extensive historic use in the treatment of bipolar disorder.

The originally proposed trademark for this product, [REDACTED], has been rejected by the Agency due to specific name confusion concerns. This decision has been accepted by Shire, and two alternative tradenames have been proposed for FDA evaluation.

There were concerns within the Division about the approval of a separately trademarked product *per se*, distinct from concerns related to a specific trademark. At one time CDER policy opposed multiple branding, but a number of exceptions to this policy have been allowed. This premeeting and meeting were held to discuss current Agency policy both internally and with the firm, and determine ramifications and next steps.

Premeeting. In the premeeting it was determined that the current Agency policy appears to be to allow the proposals for multiple trademarks to go forward in principle, evaluating each proposal for safety concerns only. Therefore, the trademark proposal EQUETRO will be evaluated by DMETS (see below).

Meeting with Firm. The firm was apprised of current policy. The submitted trademarks (EQUETRO and [REDACTED]) were discussed. [REDACTED] was rejected by DDMAC because of its similarity to a Spanish word meaning [REDACTED]. EQUETRO was not rejected by DDMAC and will be evaluated by DMETS.

The firm also included in its briefing document a set of mockups related to risk management for the new trademark (patient and healthcare provider education). DMETS will evaluate this information, but noted that it was preliminary in nature.

A recommendation on the acceptability of EQUETRO, and comments on the risk management plan materials made available, will be complete prior to the action due date of December 13, 2004.

Please see electronic signature page

Doris J. Bates, Ph.D., RPM
For the attendees

MINUTES OF MEETING WITH FIRM
Carbatrol (Acute Mania, Bipolar Disorder), IND 59,050
Shire Pharmaceutical Development Inc. / []
Type B (Pre-sNDA) Meeting

DATE: November 1, 2001

LOCATION: WOC II Rm. 4034

PARTICIPANTS: Shire: N. Frazer, R. Kishore, M. McLoudrey, M. O'Donnell, L. Shi, Y. Zhang
[]

FDA: R. Katz, T. Laughren, E. Hearst, J. Racoosin, R. Baweja, R. Kavanagh, Y.-L. Shen, D. Bates

Background: Shire holds two INDs and one approved NDA for carbamazepine products in HFD-120.

Application	Number	Active Since	Indication
IND	38,793	January 31, 1992	epilepsy
IND	59,050	September 30, 1999	bipolar disorder (acute mania)
NDA	20,712	September 30, 1997 (Approved)	epilepsy

The firm requested a pre-sNDA meeting to discuss a planned submission for treatment of acute mania associated with bipolar disorder (anticipated submission date, 1Q 2002). A briefing book was submitted on October 1, 2001.

Discussion: The course of discussion followed the sequence of questions as presented in the briefing book. These questions and the Agency responses are summarized below.

Questions, Briefing Book

1. Based on the results of study no. 105.301, and pending the results of study no. 105.302, does FDA agree that submission of these data will represent an adequate safety and efficacy package for this indication?

FDA Response. The studies in question were discussed. FDA noted that study 302, which examines the efficacy of Carbatrol in treatment of patients refractory to lithium, has a relatively small N (30 patients per treatment arm), while study 301, which is a more general efficacy study, has N = 100 patients per arm. FDA also inquired about Shire's plans for studying the long-term efficacy of the drug.

Shire explained their belief, re study 302, that the population of patients refractory to lithium experience more severe disease and are less likely to exhibit a placebo response, thus should show a greater effect size. Shire also explained that study 301 has a six month open-label continuation phase.

FDA explained that two positive, well-controlled short-term efficacy trials would be acceptable for the acute indication, but that well-controlled long-term studies should also be designed and conducted to establish long-term efficacy. A placebo-controlled relapse prevention design would be necessary; open-label continuation will not suffice. However, the long-term studies could be undertaken as a phase 4 commitment, assuming adequate short-term studies are submitted initially.

FDA also explained that the labeling language will need to reflect what is known about both short and long-term efficacy; this will be a matter of review. Shire indicated that they did not necessarily anticipate continuous use of the drug, but could foresee the possibility of drug holidays and repeated administration as patients' mood cycles required.

2. Does FDA concur with the proposed statistical analysis plan?

FDA Response. FDA observed that the study synopsis for study 301 did not appear to include any correction for center effects. Shire clarified that center was adjusted in both studies 301 and 302. However, only the centers in study 302 would be pooled due to the small number of patients randomized at each center.

FDA requested information on the pooling algorithm as part of the submission. FDA also requested Shire to include, in the submission, information on any pattern observed for missing data, and on how missing data are handled.

3. Does FDA concur with the use of Drug-Drug interaction studies from open literature sources to support the application?

FDA Response. This is acceptable. Legible copies of articles should be included in Section 6 (Human Pharmacokinetics and Bioavailability) of the submission. Search and selection criteria for submitted articles should also be included.

FDA is particularly interested in the interaction of carbamazepine with other drugs used in the treatment of bipolar disorder.

4. We believe that the proposed combination of information will provide an adequate efficacy discussion. Does FDA concur?

FDA Response. Assuming that studies 301 and 302 provide adequate evidence of efficacy, FDA would request maintenance studies as a phase 4 commitment.

5. We believe that the proposed combination of information will provide an adequate safety discussion. Does FDA concur?

FDA Response. The ISS should include serious adverse events and discontinuations due to adverse events, sorted by preferred term, treatment assignment and body system. With reference to the outline provided by Shire, Section 8.5.1. should include a similarly sorted tabulation.

FDA is also more interested in seeing AE data sorted as mild / moderate / severe rather than unrelated / possibly related / related. Narrative information should be included for all deaths, SAEs, and terminations due to AEs. (Note: Shire indicated that there were no deaths to date in these studies.)

With regard to long term safety, FDA requested an updated (via FOI) report of post-marketing AE reports for Tegretol XR. Shire and [] were also advised to seek original data in cases where they might wish to depend on literature reports, since these typically focus on efficacy and do not report safety information extensively.

Shire also confirmed that there will be a safety update from the 6-month open-label extension period which, to date, includes a total of 90 patients, with 26 having completed the full 6 months of treatment. Information on 23 more patients X 6 months open-label treatment will be available for the safety update.

6. We intend to file this sNDA electronically. The electronic submission will be formatted to be fully compliant with FDA requirements per [the] FDA Guidance [on General Considerations for Electronic Submissions to New Drug Applications]. Does FDA concur with this plan?

FDA Response. FDA representatives explained that literature articles should be included electronically for archiving so that all disciplines could access them centrally. The ISS, ISE, and clinical study reports should be provided in .pdf format for clinical and safety review access, with CRTs provided as SAS transport files. For Biopharmaceutics review, if an electronic submission is made, hyperlinks from/to Section 6 (the Human Pharmacokinetics and Bioavailability section) can be used to minimize duplication of information in/from clinical sections, but all pharmacokinetically and/or pharmacodynamically relevant information should be accessible to the Biopharm reviewer, including drug interaction information and PK/PD data for analysis. However, for statistics, paper copies of study reports will suffice, if desired, as long as the SAS files provided with the submission include the raw data.

Additional topic: Pediatric study. Shire explained that there appears to be a small population of pediatric bipolar patients for whom carbamazepine might be of benefit. Pediatric studies are intended. FDA advised the firm to study patients between the ages of [] years old, and indicated that this work could be done in Phase 4 [Post Meeting Note: this statement effectively constitutes a pediatric study deferral; under this deferral a pediatric study plan should be submitted within 120 days of the date of final approval of the application, presuming ultimate approval of same].

Conclusions / actions: The discussion concluded cordially. No slides are appended with these minutes. Submission of the supplemental NDA is anticipated, as noted, during the first quarter of 2002.

PLEASE SEE ELECTRONIC SIGNATURE PAGE.

DRS. BATES AND LAUGHREN ARE SIGNING THESE MINUTES FOR THE ATTENDEES;
DR. KATZ WILL SIGN THEM TO INDICATE ACCEPTANCE FOR DIVISION INTERNAL RECORDS
AND FOR EXTERNAL RELEASE.

NOTE: ELECTRONIC SIGNATURES WILL APPEAR ON LAST PAGE OF DOCUMENT,
FOLLOWING ANY ATTACHMENTS.

Doris J. Bates, Ph.D.
Regulatory Project Manager

Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drugs Group

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates
11/29/01 03:04:00 PM

Thomas Laughren
11/30/01 07:57:24 AM

Russell Katz
11/30/01 08:40:28 AM

Shire Pharmaceutical Development Inc
1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

17 November 2004



Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Building II
1451 Rockville Pike
Rockville, MD 20852

NDA# 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Other (Change of Company Name/Address)
Submission No: 015

Dear Dr. Katz:

Effective 01 December 2004, Shire Development Inc. will assume sponsorship of all investigational studies previously carried out by Shire Pharmaceutical Development Inc. (located at 1801 Research Blvd, Suite 600, Rockville, MD 20850).

All future correspondence regarding the above-referenced application should be addressed to:

Shire Development Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087

Please do not hesitate to contact me at (484) 595-8373 if you have any questions regarding this submission.

Sincerely,

A handwritten signature in cursive script that reads "Charles A. LaPree".

Charles A. LaPree, RAC
Senior Director, Regulatory Affairs

10 November 2004

RECEIVED
NOV 12 2004
DDR-120 / CDER

Shire

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Building II
1451 Rockville Pike
Rockville, MD 20852

NDA# 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Amendment to Pending Application:
Nomenclature Safety Report (Proposed Tradename EQUETRO™)
Submission No: 014

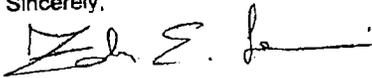
Dear Dr. Katz:

Reference is made to Shire's New Drug Application, NDA 21-710, for carbamazepine extended-release capsules, 100mg, 200mg, and 300mg.

Please find enclosed nomenclature research and analyses report for the proposed name EQUETRO as discussed during the face-to-face meeting with the Agency on 9 November 2004.

If you have any questions regarding this submission, please contact me at (484) 594-8364.

Sincerely,



Zohra Lomri
Senior Manager
Regulatory Affairs

Shire Pharmaceutical Development Inc
1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

8 November 2004

The Shire logo consists of the word "Shire" in a bold, sans-serif font. A stylized, curved line or swoosh starts under the 'S', goes up and over the 'h', and then curves down and under the 'e'.

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Building II
1451 Rockville Pike
Rockville, MD 20852

NDA# 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Amendment to Pending Application:
Response to CMC Reviewer Comments
Submission No: 013

Dear Dr. Katz:

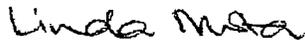
We refer you to Shire's original New Drug Application (NDA# 21-710) for carbamazepine extended-release capsules, 100mg, 200mg, and 300mg.

As requested by the Chemistry Reviewer, Dr. Chhagan Tele, Shire hereby commits to revise the bottle labelling to read:

[] (carbamazepine)
Extended-Release Capsules

If you have any questions regarding this submission, please contact me at (484) 594-8364.

Sincerely,



for Zohra Lomri
Senior Manager
Regulatory Affairs

Bates, Doris J

From: Bates, Doris J
Sent: Friday, October 29, 2004 2:46 PM
To: Bates, Doris J; 'Lomri, Zohra'
Subject: RE: NDA 20-710: Patent Certification Decision

From: Bates, Doris J
Sent: Friday, October 29, 2004 2:45 PM
To: Bates, Doris J; 'Lomri, Zohra'
Subject: RE: NDA 20-710: Patent Certification Decision

Dear Ms. Lomri,

This e-mail confirms that the Agency has reviewed your response to our 74-day letter with respect to patent certification for NDA 21-710. We have concluded that it is acceptable for you to retain the references to Carbatrol and to Tegretol as presented in your original submission. We withdraw the request for certification to Tegretol XR.

This email may be considered an official Agency communication. A copy will be placed in the FDA document archives for this NDA.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

10/29/04 02:54:32 PM

CSO

Firm notified by voice mail prior to transmission of email.

Bates, Doris J

From: Bates, Doris J

Sent: Friday, October 29, 2004 4:14 PM

To: Bates, Doris J

Subject: NDA 21-710, Telephone Call to Charles LaPree regarding Patent Certification

This email documents that I spoke with the above cited representative of Shire Laboratories on October 29 at 4:05 PM, and informed him that the patent certification provided with the original NDA submission had been determined to be sufficient. I clarified that this meant that we no longer wanted Shire to certify their product against Tegretol XR, but that the original patent certifications to Carbatrol and Tegretol were sufficient.

Mr. LaPree thanked me for this information and the teleconference concluded cordially.

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research*

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates
10/29/04 04:16:45 PM
CSO

Shire Pharmaceutical Development Inc
1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

27 October 2004



Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

NDA#: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Amendment to Pending Application:
Response to Clinical Reviewer Comments of 1 October 2004
Submission No: 010

Dear Dr. Katz,

We refer you to Shire's original New Drug Application (NDA# 21-710) for carbamazepine extended-release capsules, 100mg, 200mg, and 300mg, the subject of IND #59,050.

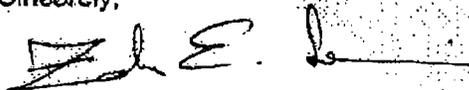
On 1 October 2004, Dr. Bates forwarded via email the following comments from Dr. Robert Levin (Clinical Reviewer).

1. Please provide the mean and median doses used in the controlled studies.
2. Please provide outlier analyses for the particular ECG parameters (QT, QTcB, QRS, etc.).
3. Please provide documents pertaining to financial disclosure (or direct us to where we might find it in the current submission).

Please note this information has been forwarded to Dr. Bates and Dr. Levin via secure email.

If you have any questions regarding this submission, please contact me at (484) 594-8384.

Sincerely,



Zohra Lomri, MS
Senior Manager
Regulatory Affairs



26 October 2004

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

NDA No: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Amendment to Pending Application:
Briefing Document for Type A Meeting
Submission No: 009

Dear Dr. Katz:

We refer you to Shire's original New Drug Application (NDA# 21-710) for carbamazepine extended-release capsules, 100mg, 200mg, and 300mg, the subject of IND # 59,050, and to your recommendation regarding the use of an alternate brand name for SPD417 dated on 04 October 2004.

Please find enclosed briefing document for a Type A Meeting to discuss an alternative risk management/communication plan.

If you have any questions regarding this submission, please contact me at (484) 595-8364.

Sincerely,


Zohra Lomri, MS
Senior Manager
Regulatory Affairs

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: November 8, 2004	DESIRED COMPLETION DATE: December 9, 2004	ODS CONSULT #: 04-0285
DATE OF DOCUMENT: October 26, 2004	PDUFA DATE: December 9, 2004	

TO: Russell Katz, MD
 Director, Division of Neuropharmacological Drug Products
 HFD-120

THROUGH: Doris Bates, PhD.
 Project Manager
 HFD-120

PRODUCT NAME: Equetro (Carbamazepine Extended-release Capsules) 100 mg, 200 mg, and 300 mg	NDA SPONSOR: Shire Pharmaceutical Development, Inc.
NDA#: 21-710 (IND# 59,050)	

SAFETY EVALUATOR: Linda M. Wisniewski, RN

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Equetro. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name, and its associated labels and labeling must be re-evaluated. A re-review of the name and its associated labels and labeling will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
2. DDMAC finds the proprietary name Equetro acceptable from a promotional perspective.

Denise Toyer, PharmD.
 Deputy Director
 Division of Medication Errors and Technical Support
 Office of Drug Safety
 Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, RPh
 Director
 Division of Medication Errors and Technical Support
 Office of Drug Safety
 Phone: (301) 827-3242 Fax: (301) 443-9664

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 19, 2004

NDA #: 21-710 (IND# 59,050)

NAME OF DRUG: **Equetro** (Carbamazepine Extended-release Capsules)
100 mg, 200 mg, and 300 mg

NDA HOLDER: Shire Pharmaceutical Development, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for assessment of the proprietary name Equetro, regarding potential name confusion with other proprietary or established names. The sponsor proposes to market their Carbamazepine Extended-release Capsules product for a new indication of use, acute mania due to bipolar disorder, under the proprietary name Equetro. The sponsor currently markets Carbatrol (Carbamazepine Extended-release Capsules), which has been marketed since its approval on September 30, 1997, for use in epilepsy and trigeminal neuralgia (NDA 20-712). This is the second name review for this application. The sponsor previously submitted the proposed proprietary name Equetro for review and comment and had submitted a justification for dual tradenames. The name Equetro was evaluated and found unacceptable in DMETS consult 04-0081. Additionally, DMETS evaluated the justification for dual tradenames and expressed concern for the possibility of double prescribing between patients with both indications of use, and as a result, did not recommend use of dual tradenames. DMETS participated in a meeting on November 9, 2004 with the sponsor and the Division of Neuropharmacological Drug Products, at which time it was decided that dual tradenames for this particular product were acceptable because there appeared to be no safety concerns with dual prescribing or dose related side effects. However, the Division agreed with DMETS that Equetro was not an acceptable name from a sound and look-alike perspective. Therefore, the firm submitted this name, Equetro, for review and comment. Revised draft container labels, carton and insert labeling were not provided for review and comment with this request.

PRODUCT INFORMATION

Equetro is the proposed proprietary name for Carbamazepine Extended-Release Capsules, indicated for the treatment of acute mania due to bipolar disorder. The usual recommended adult dosage of Equetro is 400 mg daily in divided doses, twice daily to start, and increasing to 1600 mg daily if necessary. The sponsor proposes to market Equetro in 100 mg, 200 mg, and 300 mg extended-release capsules in bottles of 100's.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Equetro to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Equetro. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Equetro acceptable from a promotional perspective.
2. The Expert Panel identified six proprietary names that were thought to have the potential for confusion with Equetro. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

Appears This Way
On Original

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], Drugs@FDA, the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose	Other**
Equetro	Carbamazepine Extended-release Tablets 100 mg, 200 mg, 300 mg	200 mg to 800 mg twice daily	N/A
Ecotrin	Aspirin Enteric-Coated Tablets 81 mg, 325 mg, 500 mg	81 mg to 1000 mg every four to six hours.	SA
Ecando***	50 mg For Injection	100 mg loading dose on day 1, followed by 50 mg daily thereafter. The rate of infusion should not exceed 1.1 mg/minute.	SA
Equanil	Meprobamate Tablets 200 mg, 400 mg Tablets 400 mg Capsule	200 mg or 400 mg three or four times a day. Maximum dose 2.4 g daily.	LA/SA
Epoetin	2000 units, 3000 units, 4000 units, 10000 units, 20000 units, 40000 units	12.5 units to 52.5 units/kg/day.	LA
Concerta	Methylphenidate HCl Extended-release Tablets 18 mg, 27 mg, 36 mg, and 54 mg	18 mg to 72 mg q day.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) *** Pending review. Not FOI.			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Equetro were discussed by the Expert Panel.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Equetro with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 125 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Equetro (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p style="text-align: center;"><u>Outpatient RX:</u></p> <p style="text-align: center;">Equetro TPO qid #120</p>	<p>Equetro</p> <p>Take one four times a day</p> <p>Dispense #120</p>
<p><u>Inpatient RX:</u></p> <p style="text-align: center;">Equetro 1/31/14 #120 <i>Antonio M. P. Calais</i></p>	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Equetro, the primary concerns related to look-alike and sound-alike confusion with Ecotrin, Ecando, τ Equanil, Epoetin, and Concerta.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name.

1. Ecotrin may sound similar to Equetro when spoken. Ecotrin is an enteric-coated aspirin tablet indicated for the relief of minor aches and pains and fever reduction. Both names contain three syllables, and begin with letters that may sound similar (ec vs. eq). However, the endings (tro vs. trin) are phonetically different despite sharing the 'tr' sound. Additionally, there are characteristics that may help to differentiate these two products. They include the strength (100 mg, 200 mg, and 300 mg vs. 81 mg, 325 mg, and 500 mg), frequency of administration (twice daily vs. once daily or every four to six hours), and indication of use (acute mania with bipolar disorder vs. pain and fever). Although an individual dose may overlap at 500 mg, the frequency of administration would help to differentiate these two products in addition to the different phonetic endings of Ecotrin and Equetro. These characteristics will help to differentiate these two products and minimize confusion.

2. Ecando^{***} may sound similar to Equetro when spoken. Ecando is indicated for the treatment of esophageal candidiasis and is the subject of a pending New Drug Application (NDA # 21-632). An approvable action was taken on this NDA on May 21, 2004. Therefore, DMETS must evaluate potential confusion with this name since the final disposition of this proprietary name has not been determined. Both names contain three syllables and begin and end with similar sounding letters (eque vs. eca and do vs. tro) which contributes to the phonetic similarities. However, there are product characteristics that may help to differentiate them. They include such things as dose (200 mg to 800 mg vs. 100 mg and 50 mg), dosage form (tablet vs. injection), strength (100 mg, 200 mg, and 300 mg vs. 50 mg), frequency of administration (twice daily vs. once daily), route of administration (oral vs. intravenous), indication of use (acute mania with bipolar disorder vs. esophageal candidiasis), and storage location (oral solids vs. injectables). The differentiating product characteristics will help to minimize confusion between this name pair.

3. 

4. Equanil may look and sound similar to Equetro when written or spoken. Equanil is indicated in the treatment of anxiety. Both names contain three syllables and begin with the same three letters (equ). However, the endings of each name are phonetically and orthographically different (nil vs. tro). Although both names contain upstrokes (t vs. l), they are in different locations, which may also help to distinguish the names when written (see page 7). The frequency of administration (twice daily vs. three or four times daily) may also help to differentiate these two products. Although some strengths (200 mg

^{***} NOTE: This review contains proprietary and confidential information that should not be released to the public. ^{***}

and 400 mg vs. 100 mg, 200 mg, 300 mg) and individual doses may overlap (200 mg or 400 mg), the frequency of administration and the orthographic and phonetic differences in the endings of the names will help to minimize confusion.

Epoetin
Equetro

5. Epoetin may look similar to Equetro when written. Epoetin is indicated in the treatment of anemia. Both names begin and end with letters that may look similar when scripted (epoe vs. eque and tin vs. tro). Despite the orthographic similarities (see below), there are product characteristics that may help to differentiate them. They include the dose (200 mg to 800 mg vs. 12.5 units/kg/day to 52.5 mg/kg/day), dosage form (tablet vs. injection), strength (100 mg, 200 mg, and 300 mg vs. 2000 units, 3000 units, 4000 units, 10000 units, 20000 units, and 40000 units), frequency of administration (twice daily vs. daily to weekly), route of administration (oral vs. intravenous and subcutaneous), indication of use (acute mania with bipolar disorder vs. anemia), and storage location (oral solids vs. injectable). Despite the orthographic similarities, the product characteristics will help to minimize confusion between Epoetin and Equetro.

Epoetin
Equetro

6. Concerta may look similar to Equetro when written. Concerta is indicated in the treatment of Attention Deficit Hyperactivity Disorder. Both names begin with letters that may look similar when scripted (eque vs. con). Additionally, the ending of each name contains similarly scripted letters (tro vs. rta), despite their different placement. Despite the orthographic similarities, there are product characteristics that will help to differentiate them. They include the dose (200 mg to 800 mg vs. 18 mg to 72 mg), strength (100 mg, 200 mg, and 300 mg vs. 18 mg, 27 mg, 36 mg, and 54 mg), frequency of administration (once daily vs. twice daily), indication of use (acute mania with bipolar disorder vs. attention deficit hyperactivity disorder), and storage location (oral solids vs. with other C-II drugs with limited access). Overall, the product characteristics will help to differentiate these two products and minimize confusion.

equetro *concerta*

E. INDEPENDENT NAME ANALYSIS *⌈* *⌋*

Upon review of the information submitted by *⌈* *⌋* the following additional names were identified as potential sound or look-alike products.

1. Similar Drug Name Listing:

The names identified by *⌈* *⌋* as potential candidates for look and sound-alike similarities that were not included in the DMETS review were: Effexor, Equagesic,

Equilet, Lexapro and Questran. After further evaluation of the aforementioned names, DMETS concurs that these names do not pose a significant problem due to differentiating product characteristics, such as dosage form, frequency of administration or strength.

2. Medical Term Similarity:

Equilibrium was considered to be similar to Equetro, based on sound and/or appearance. After further review of the aforementioned medical term, DMETS concurs that this medical term does not pose a significant problem with the proposed proprietary name, Equetro.

3. Computer-Assisted Analysis:

The following nineteen names were listed for further consideration due to similarity with Equetro: Ak-Trol, Caltro, Dequasine, Detrol, Diatrol, Emetrol, E-Pilo, Equalactin, Equazine M, Estro-Cyp, Eutron, Glucotrol, Nitro-Dur, Quelicin, Quelidrine, Quetiapine Fumarate, Rebetrone, Retrovir, and Rocaltrol. After further evaluation of the aforementioned names, DMETS concurs that these names do not pose a significant problem due to differentiating product characteristics such as dosage form, frequency of administration or strength.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS reviewed the labels and labeling associated with this NDA in ODS Consult # 04-0081, dated July 9, 2004. Since the firm did not submit revised labels and labeling, we refer you to those comments.

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Equetro. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions referred to in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Equetro acceptable from a promotional perspective.

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A:

Inpatient	Outpatient	Voice
Equatuo	Equetro	Agretrol
Equestus	Equetro	Eclitro
Equetine	Equetro	Eglitro
Equetro	Equetro	Egretro
Equetro	Equetro	Equetrel
Equetro	Equetro	Equetro
Equetue	Equetro	Equistro
Equetueo	Equetro	Equitro
Equetuo	Equetro	Equitro
Equetus		Equitrol
Equitab		
Equitra		
Equitro		
Equitrol		
Equituo		

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Linda Wisniewski
12/2/04 04:09:30 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/2/04 04:17:58 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/6/04 10:17:05 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): HFD-420 (ODS/DMETS)			FROM: HFD-120 (Dr. Bates)	
DATE October 27, 2004	IND NO.59,050	NDA NO. 21-710	TYPE OF DOCUMENT new NDA submission - Proprietary name consult (2 new names)	DATE OF DOCUMENT Oct. 26, 2004
NAME OF DRUG carbamazepine		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG antimanic	DESIRED COMPLETION DATE: Action due date December 13, 2004 Meet w. firm November 9, 2004. Trademark consult feedback requested by December 9, 2004
NAME OF FIRM: Shire Pharmaceutical Development, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS:				
<p>This supersedes the previously re-submitted consult for the proposed trademark []. In the attached document, Shire proposes two new alternative trademarks to take the place of []. These proposed trademarks are EQUETRO (first choice) and [] (second choice).</p> <p>No new information has been received from the firm regarding revisions to the PI or labels at this time. The attached briefing book includes mockups of some elements for a risk management proposal to address any alternative trademark. I have checked the EDR and there is no new information there pertinent to this submission.</p>				
SIGNATURE OF REQUESTER see DFS signature			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

10/27/04 02:40:45 PM

Courtesy DFS copies to DMETS. of consult form only.
Briefing book submitted as hard copy. Sufficient copies
are being forwarded for all DMETS invitees to
11/9/04 meeting.

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Monday, October 25, 2004 6:06 PM
To: 'Bates, Doris J'; 'Levin, Robert'; Mota, Linda
Subject: RE: NDA 21-710: Questions, Clinical Reviewer



Response 2 to response 2 to
01 oct question .01 oct question .

Good evening,

Attached is the data requested for question 2 in 2 separate attachments. A hard copy will be sent to you as well, Again, I apologize for the delay.

Regards

<<Response 2 to 01 oct question part 1.doc>> <<response 2 to 01 oct question part 2.doc>>

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

-----Original Message-----

From: Lomri, Zohra
Sent: Friday, October 22, 2004 2:58 PM
To: 'Bates, Doris J'; Levin, Robert; Mota, Linda
Subject: RE: NDA 21-710: Questions, Clinical Reviewer

Good afternoon,

Attached is the data requested for question 1. A hard copy will be sent to you on Monday. The remaining information will be forwarded to you on Monday.

I apologize for the delay.

Feel free to contact me at your earliest convenience if you need anything.

<< File: response 1 to 01 oct question.doc >>

Kind regards

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Friday, October 01, 2004 10:22 AM
To: Lomri, Zohra
Cc: Bates, Doris J; Levin, Robert
Subject: RE: NDA 20-712: Questions, Clinical Reviewer

Good morning Zohra:

Our clinical reviewer would like to request a few more items of information:

1. Please provide the mean and median doses used in the controlled studies.
2. Please provide outlier analyses for the particular ECG parameters (QT, QTcB, QRS, etc.).
3. Please provide documents pertaining to financial disclosure (or direct us to where we might find it in the current submission).

I am including our reviewer as a CC recipient on this e-mail. You may wish to include him as a CC recipient on your reply, to speed his receipt of the information if I am out of the office or in meetings when the information arrives. Any new information submitted in response should also be submitted to the NDA in the format appropriate to its section, but we can work with information sent by e-mail before the official submission arrives.

Thanks as always,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Please provide outlier analyses for the particular ECG parameters (QT, QTcB, QRS, etc.)

The criteria listed in Table 1 were used to provide the outlier analyses for the specified ECG parameters.

Table 1: Outlier Criteria for ECG Parameters	
Test	Criteria
Heart Rate	≤ 40 beats/min or ≥ 120 beats/min
PR Interval	≥ 200 msec
QT Interval	≥ 480 msec
QRS Interval	≥ 120 msec
QTc	≥ 500 msec

Table 2 is a listing of all patients that had normal baseline ECG parameters and an out-of-range value at endpoint. Seven (7) subjects in the short-term Carbamol group had out-of-range endpoint values, 6 subjects had PR Interval increases and 1 subject had decreased ventricular rate. There were no patients in the short-term Carbamol group that met criteria for QRS, QT, or QTc out-of-range endpoints.

Six (6) subjects in the short-term placebo group had out-of-range endpoint values, 4 subjects had PR Interval increases and 2 subjects had QRS Interval increases. There were no patients in the short-term placebo group that met criteria for ventricular rate, QT, or QTc out-of-range endpoints.

Five (5) subjects in the long-term Carbamol group had out-of-range endpoint values, 4 subjects had PR Interval increases and 1 subject had QRS Interval increases. There were no subjects in the long-term Carbamol group that met criteria for ventricular rate, QT, or QTc out-of-range endpoints.

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On Original**

Table 2: List of Subjects with Normal Value at Baseline and Out-of-Range Value at Endpoint

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Carbatrol: short-term	105.301-001-013	Baseline	55	170	100	410	393
		Endpoint	77	201*	78	386	437
	105.301-004-007	Baseline	47	180	110	450	398
		Endpoint	55	200*	110	420	402
	105.301-028-012	Baseline	68	180	90	380	405
		Endpoint	69	200*	90	370	397
	105.302-034-204	Baseline	52	150	90	420	391
Endpoint		33*	190	90	450	334	
417.304-006-002	Baseline	60	190	90	390	390	
	Endpoint	63	220*	100	390	400	
417.304-023-001	Baseline	56	190	90	410	396	
	Endpoint	84	230*	90	340	402	
417.304-051-021	Baseline	71	190	80	340	370	
	Endpoint	63	230*	100	390	400	
Placebo: short-term	105.301-019-005	Baseline	61	190	100	420	423
		Endpoint	68	240*	90	390	415
	105.301-029-005	Baseline	72	160	100	370	405
		Endpoint	81	200*	110	340	395
	105.301-030-010	Baseline	48	170	90	410	367
		Endpoint	45	200*	100	440	381
417.304-012-006	Baseline	70	190	90	360	389	
	Endpoint	71	200*	100	390	424	
417.304-018-009	Baseline	71	200	110	340	370	
	Endpoint	77	190	120*	340	385	
417.304-024-007	Baseline	61	160	110	380	383	
	Endpoint	62	170	120*	370	376	
Carbatrol: long-term	105.303-005-002	Baseline	59	190	100	430	426
		Endpoint	46	200*	90	410	359
	105.303-005-007	Baseline	63	180	100	410	420
		Endpoint	65	200*	100	400	416
	105.303-030-013	Baseline	78	160	100	350	399
Endpoint		66	200*	100	380	399	
105.303-030-204	Baseline	60	180	90	370	370	
	Endpoint	50	210*	100	410	374	
105.303-035-202	Baseline	62	180	100	380	386	
	Endpoint	81	170	120*	350	407	

* Value meets defined outlier criteria.

For heart rate, only 1 subject (0.4%) in the short-term studies on Carbatrol had a drop below 40 BPM that had been between 40 and <120 at baseline. There were no other subjects below 40 or above 120 BPM for the short-term placebo groups or long-term Carbatrol groups. (Table 3)

Table 3: Ventricular Rate - Change from Baseline to Endpoint in Phase 3 Studies						
		End-Study				
Treatment Group	Ventricular Rate (BPM) Baseline	NA	< 40	40 - < 120	>= 120	Total
Short-Term Studies: Carbatrol	Not Available (NA)	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	2
	< 40	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	40 - < 120	31 (12.4%)	1 (0.4%)	217 (87.1%)	0 (0.0%)	249
	>= 120	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	Total	32	1	218	0	251
Short-Term Studies: Placebo	NA	1 (33.3%)	0 (0.0%)	2 (66.7%)	0 (0.0%)	3
	< 40	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	40 - < 120	36 (14.7%)	0 (0.0%)	209 (85.3%)	0 (0.0%)	245
	>= 120	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	Total	37	0	211	0	248
Long-Term Study: Carbatrol	NA	2 (66.7%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	3
	< 40	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	40 - < 120	13 (14.6%)	0 (0.0%)	76 (85.4%)	0 (0.0%)	89
	>= 120	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	Total	15	0	77	0	92

Not Available (NA): Records are not available either at baseline or endpoint

For PR intervals, 6 subjects (2.5%) in the short-term Carbatrol group, 4 subjects (4.7%) in the short-term placebo group, and 4 subjects (4.7%) in the long-term Carbatrol group had PR intervals \geq 200 msec, with a baseline PR interval < 200 msec. (Table 4)

Table 4: PR Interval – Change from Baseline to Endpoint in Phase 3 Studies					
		End-Study			
Treatment Group	PR Interval (msec) Baseline	NA	< 200	>= 200	Total
Short-Term Studies: Carbatrol	Not Available (NA)	3 (75.0%)	1 (25.0%)	0 (0.0%)	4
	< 200	30 (12.7%)	200 (84.7%)	6 (2.5%)	236
	>= 200	1 (9.1%)	5 (45.5%)	5 (45.5%)	11
	Total	34	206	11	251
Short-Term Studies: Placebo	NA	1 (25.0%)	3 (75.0%)	0 (0.0%)	4
	< 200	35 (15.2%)	192 (83.1%)	4 (1.7%)	231
	>= 200	1 (7.7%)	6 (46.2%)	6 (46.2%)	13
	Total	37	201	10	248
Long-Term Study: Carbatrol	NA	2 (66.7%)	1 (33.3%)	0 (0.0%)	3
	< 200	13 (15.1%)	69 (80.2%)	4 (4.7%)	86
	>= 200	0 (0.0%)	2 (66.7%)	1 (33.3%)	3
	Total	15	72	5	92

Not Available (NA): Records are not available either at baseline or endpoint

For the QRS interval, no subjects (0.0%) in the short-term Carbatrol group, 2 subjects (0.8%) in the short-term placebo group, and 1 subject (1.1%) in the long-term Carbatrol group had QRS intervals that were ≥ 120 msec, with baseline QRS intervals < 120 msec. (Table 5)

Treatment Group	QRS Interval (msec) Baseline	End-Study			Total
		NA	< 120	≥ 120	
Short-Term Studies: Carbatrol	Not Available (NA)	1 (50.0%)	1 (50.0%)	0 (0.0%)	2
	< 120	30 (12.1%)	217 (87.9%)	0 (0.0%)	247
	≥ 120	1 (50.0%)	0 (0.0%)	1 (50.0%)	2
	Total	32	218	1	251
Short-Term Studies: Placebo	NA	1 (33.3%)	2 (66.7%)	0 (0.0%)	3
	< 120	36 (14.9%)	204 (84.3%)	2 (0.8%)	242
	≥ 120	0 (0.0%)	0 (0.0%)	3 (100%)	3
	Total	37	206	5	248
Long-Term Study: Carbatrol	NA	2 (66.7%)	1 (33.3%)	0 (0.0%)	3
	< 120	12 (13.8%)	74 (85.1%)	1 (1.1%)	87
	≥ 120	1 (50.0%)	0 (0.0%)	1 (50.0%)	2
	Total	15	75	2	92

Not Available (NA): Records are not available either at baseline or endpoint

For those subjects having end of study ECG, there were no subjects (0.0%) from any treatment group exhibiting QT interval readings ≥ 480 msec, with baseline readings < 480 msec.

For those subjects having end of study ECG, there were no subjects (0.0%) from any treatment group exhibiting QTc Bazett readings ≥ 500 msec, with baseline readings < 500 msec.

Qualitative changes in QT Interval and QTc Bazett are presented for the short and long-term trials in Table 6 and Table 7. For QT intervals 6 subjects (2.4%) in the short-term Carbatrol group, 13 subjects (5.2%) in the placebo group, and 1 subject (1.1%) in the long-term Carbatrol group had a greater than or equal to 60 msec change from baseline to endpoint. For QTc Bazett 5 subjects (2.0%) in the short-term Carbatrol group, 2 subjects (0.8%) in the placebo group, and no subjects (0.0%) in the long-term Carbatrol group had a greater than or equal to 60 msec change from baseline to endpoint.

Table 6: Qualitative Change in QT Interval and QTc Bazett Recorded in Phase 3 Short-term Studies (105.301, 105.302, and 417.304)		
Change from Baseline to Endpoint	Treatment Group	
	Carbatrol	Placebo
QT Interval (msec)		
Not Available (NA)	33 (13.1%)	40 (16.1%)
< 0	102 (40.6%)	89 (35.9%)
0 - <30	70 (27.9%)	76 (30.6%)
30 - <60	40 (15.9%)	30 (12.1%)
>= 60	6 (2.4%)	13 (5.2%)
Total	251	248
QTc Bazett (msec)		
NA	33 (13.1%)	40 (16.1%)
< 0	115 (45.8%)	100 (40.3%)
0 - <30	82 (32.7%)	75 (30.2%)
30 - <60	16 (6.4%)	31 (12.5%)
>= 60	5 (2.0%)	2 (0.8%)
Total	251	248
Not Available (NA): Records are not available either at baseline or endpoint		

Table 7: Qualitative Change in QT Interval and QTc Bazett Recorded in Phase 3 Long-term Study (105.303)	
Change from Baseline to Endpoint	Treatment Group
	Carbatrol
QT Interval (msec)	
Not Available (NA)	16 (17.4%)
< 0	30 (32.6%)
0 - <30	32 (34.8%)
30 - <60	13 (14.1%)
>= 60	1 (1.1%)
Total	92
QTc Bazett (msec)	
NA	16 (17.4%)
< 0	31 (33.7%)
0 - <30	34 (37.0%)
30 - <60	11 (12.0%)
>= 60	0 (0.0%)
Total	92
Not Available (NA): Records are not available either at baseline or endpoint	

Listings of subjects with increases ≥ 30 for QT Interval or QTC Bazette in Phase III studies are provided as an attachment to this response.

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Short-term Studies (105.301, 105.302, 417.304)

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Carbatrol	105.301-001-010	Baseline	101	140	90	330	428
		Endpoint	81	190	90	370*	430
	105.301-001-013	Baseline	55	170	100	410	393
		Endpoint	77	201	78	386	437*
	105.301-015-004	Baseline	63	160	100	380	389
		Endpoint	80	140	100	380	439*
	105.301-017-003	Baseline	61	170	90	370	373
		Endpoint	45	180	100	420*	364
	105.301-024-003	Baseline	73	150	100	360	397
		Endpoint	77	150	100	400*	453*
	105.301-024-013	Baseline	55	150	100	370	354
		Endpoint	50	120	100	410*	374
	105.301-024-019	Baseline	71	170	90	360	392
		Endpoint	78	150	100	370	422*
	105.301-025-004	Baseline	101	133	81	346	449
		Endpoint	80	170	90	380*	439
	105.301-027-020	Baseline	72	190	90	360	394
		Endpoint	49	180	90	400*	361
	105.301-028-005	Baseline	62	190	90	330	335
		Endpoint	66	180	100	350	367*
	105.301-028-013	Baseline	78	150	100	390	445
		Endpoint	65	180	100	440*	458

(Continued)

* = increases ≥ 30 - < 60 and ** = increases ≥ 60

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Short-term Studies (105.301, 105.302, 417.304) - Continued

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Carbatrol	105.301-028-017	Baseline	63	170	100	360	369
		Endpoint	75	160	110	400*	447**
	105.301-031-008	Baseline	109	110	90	280	377
		Endpoint	100	120	90	330*	426*
	105.301-034-003	Baseline	101	140	100	340	441
		Endpoint	66	180	90	380*	399
	105.302-020-201	Baseline	68	150	90	380	405
		Endpoint	50	160	100	430*	393
	105.302-028-209	Baseline	75	140	100	360	402
		Endpoint	65	160	100	400*	416
	105.302-030-204	Baseline	74	180	90	320	355
		Endpoint	60	180	90	370*	370
	105.302-030-214	Baseline	100	180	80	340	439
		Endpoint	76	190	90	390*	439
	105.302-034-204	Baseline	52	150	90	420	391
		Endpoint	33	190	90	450*	334
	417.304-002-003	Baseline	68	160	90	380	405
		Endpoint	76	140	90	390	439*
	417.304-003-012	Baseline	78	150	90	370	422
		Endpoint	101	170	100	350	454*
	417.304-003-014	Baseline	49	200	90	390	352
		Endpoint	61	190	100	390	393*

(Continued)

* = increases ≥ 30 - < 60 and ** = increases ≥ 60

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazetti in Phase 3 Short-term Studies (105.301, 105.302, 417.304) - Continued

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Carbatrol	417.304-006-008	Baseline	86	150	90	370	443
		Endpoint	61	190	100	410*	413
	417.304-012-019	Baseline	75	180	80	350	391
		Endpoint	68	180	80	380*	405
	417.304-013-002	Baseline	95	200	80	330	415
		Endpoint	75	220	90	370*	414
	417.304-018-008	Baseline	56	180	100	370	357
		Endpoint	89	170	90	330	402*
	417.304-018-012	Baseline	80	160	90	370	427
		Endpoint	68	180	90	400*	426
	417.304-020-014	Baseline	77	160	100	350	396
		Endpoint	74	170	90	380*	422
	417.304-024-005	Baseline	53	160	90	410	385
		Endpoint	90	160	90	350	429*
	417.304-024-008	Baseline	69	130	100	370	397
		Endpoint	69	160	100	410*	440*
	417.304-051-011	Baseline	88	130	100	310	375
		Endpoint	63	140	80	360*	369
	417.304-051-014	Baseline	76	140	100	370	416
		Endpoint	68	140	90	400*	426
	417.304-051-017	Baseline	107	160	100	310	414
		Endpoint	81	170	100	350*	407

(Continued)

* = increases ≥ 30 - < 60 and ** = increases ≥ 60

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Short-term Studies (105.301, 105.302, 417.304) - Continued

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Carbatrol	417.304-051-019	Baseline	77	160	100	360	408
		Endpoint	52	160	100	400*	372
	417.304-051-021	Baseline	71	190	80	340	370
		Endpoint	63	230	100	390*	400*
	417.304-051-025	Baseline	98	140	90	300	383
		Endpoint	71	140	90	340*	370
	417.304-051-026	Baseline	107	130	90	310	414
		Endpoint	75	130	80	350*	391
	417.304-053-002	Baseline	57	100	90	390	380
		Endpoint	56	150	100	430*	415*
	417.304-053-005	Baseline	83	190	90	320	376
		Endpoint	78	170	100	360*	410*
	417.304-053-012	Baseline	90	150	90	350	429
		Endpoint	70	170	90	380*	410
	417.304-053-014	Baseline	103	130	100	290	380
		Endpoint	100	140	80	330*	426*
	417.304-053-026	Baseline	98	160	80	330	422
		Endpoint	70	160	90	370*	400
	417.304-054-003	Baseline	82	150	100	360	421
		Endpoint	68	160	100	400*	426
	417.304-054-007	Baseline	78	180	90	370	422
		Endpoint	57	150	90	400*	390

(Continued)

* = increases ≥ 30 - < 60 and ** = increases ≥ 60

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Short-term Studies (105.301, 105.302, 417.304) - Continued

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Carbatrol	417.304-054-013	Baseline	67	160	90	400	423
		Endpoint	56	190	100	430*	415
	417.304-054-019	Baseline	90	140	90	340	416
		Endpoint	61	160	100	390*	393
	417.304-054-027	Baseline	98	140	100	330	422
		Endpoint	62	150	100	380*	386
417.304-054-029	Baseline	113	130	100	310	425	
	Endpoint	83	150	100	340*	400	
Placebo	417.304-056-007	Baseline	72	180	110	350	383
		Endpoint	57	180	110	380*	370
	105.301-001-014	Baseline	90	180	80	340	416
		Endpoint	79	172	82	392*	450*
	105.301-005-008	Baseline	64	180	90	360	372
		Endpoint	72	180	90	390*	427*
105.301-011-008	Baseline	57	180	100	390	380	
	Endpoint	75	180	100	370	414*	
105.301-017-002	Baseline	75	160	90	350	391	
	Endpoint	68	160	90	400*	426*	
105.301-017-006	Baseline	47	150	90	380	336	
	Endpoint	65	93	97	378	393*	
105.301-017-008	Baseline	55	160	90	380	364	
	Endpoint	68	160	110	370	394*	

(Continued)

* = increases ≥ 30 - < 60 and ** = increases ≥ 60

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Short-term Studies (105.301, 105.302, 417.304) - Continued

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Placebo	105.301-019-001	Baseline	105	170	80	320	423
		Endpoint	68	140	100	430**	458*
	105.301-019-003	Baseline	71	160	90	380	413
		Endpoint	62	150	110	450**	457*
	105.301-024-012	Baseline	83	170	90	340	400
		Endpoint	65	150	90	370*	385
	105.301-024-017	Baseline	98	150	90	360	460
		Endpoint	76	150	90	390*	439
	105.301-025-005	Baseline	63	160	100	400	410
		Endpoint	61	170	90	430*	434
	105.301-027-006	Baseline	80	160	100	340	393
		Endpoint	59	150	100	380*	377
	105.301-027-008	Baseline	86	190	90	340	407
		Endpoint	78	190	80	390*	445*
	105.301-027-018	Baseline	89	140	100	340	414
		Endpoint	77	140	110	370*	419
	105.301-028-010	Baseline	85	140	110	320	381
		Endpoint	81	190	100	360*	418*
	105.301-030-010	Baseline	48	170	90	410	367
		Endpoint	45	200	100	440*	381
	105.301-031-002	Baseline	66	140	90	400	420
		Endpoint	75	160	100	410	458*

* = increases ≥ 30 - < 60 and ** = increases ≥ 60

(Continued)

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Short-term Studies (105.301, 105.302, 417.304) - Continued

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Placebo	105.301-034-004	Baseline	53	160	100	400	376
		Endpoint	74	150	90	370	411*
	105.302-005-206	Baseline	78	180	100	320	365
		Endpoint	66	170	100	360*	378
	105.302-028-202	Baseline	65	140	100	390	406
		Endpoint	78	160	100	390	445*
	105.302-028-203	Baseline	55	180	100	360	345
		Endpoint	65	140	90	380	396*
	105.302-028-210	Baseline	61	150	110	380	383
		Endpoint	88	180	100	350	424*
	105.302-030-213	Baseline	92	190	90	340	421
		Endpoint	83	190	80	390*	459*
	105.302-030-219	Baseline	73	200	110	350	386
		Endpoint	73	180	110	400*	441*
	105.302-034-206	Baseline	68	140	80	350	373
		Endpoint	68	160	80	400*	426*
	105.302-034-207	Baseline	61	170	90	380	383
		Endpoint	78	180	90	370	422*
	417.304-001-004	Baseline	54	190	100	410	389
		Endpoint	50	190	80	450*	411
	417.304-002-004	Baseline	68	160	100	360	383
		Endpoint	53	130	110	410*	385

* = increases ≥ 30 - < 60 and ** = increases ≥ 60 (Continued)

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Short-term Studies (105.301, 105.302, 417.304) - Continued

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Placebo	417.304-006-001	Baseline	84	180	110	350	414
		Endpoint	67	170	90	390*	412
	417.304-011-009	Baseline	58	190	100	380	374
		Endpoint	47	170	90	410*	363
	417.304-012-006	Baseline	70	190	90	360	389
		Endpoint	71	200	100	390*	424*
	417.304-016-003	Baseline	60	180	80	340	340
		Endpoint	75	190	90	340	380*
	417.304-018-014	Baseline	55	160	100	390	373
		Endpoint	46	160	100	430*	377
	417.304-020-003	Baseline	54	150	90	390	370
		Endpoint	63	100	90	390	400*
	417.304-020-005	Baseline	75	140	80	350	391
		Endpoint	64	150	80	380*	392
	417.304-020-008	Baseline	65	190	100	370	385
		Endpoint	80	160	80	370	427*
	417.304-020-012	Baseline	61	130	80	380	383
		Endpoint	90	190	90	340	416*
	417.304-020-015	Baseline	100	130	100	310	400
		Endpoint	76	140	80	360*	405
	417.304-023-006	Baseline	71	140	100	360	392
		Endpoint	68	140	100	400*	426*

* = increases ≥ 30 - < 60 and ** = increases ≥ 60 (Continued)

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Short-term Studies (105.301, 105.302, 417.304) - Continued

Treatment Group	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Placebo	417.304-024-001	Baseline	60	140	100	350	350
		Endpoint	64	150	100	370	382*
	417.304-024-004	Baseline	68	230	100	310	330
		Endpoint	72	240	100	340*	372*
	417.304-024-010	Baseline	63	150	90	380	389
		Endpoint	50	150	90	420*	383
	417.304-051-020	Baseline	85	140	90	330	393
		Endpoint	75	130	90	360*	402
	417.304-053-013	Baseline	80	150	100	340	393
		Endpoint	105	160	80	320	423*
	417.304-053-015	Baseline	60	150	100	380	380
		Endpoint	61	160	100	410*	413*
	417.304-053-023	Baseline	68	160	90	350	373
		Endpoint	103	140	100	320	419*
	417.304-054-006	Baseline	74	200	100	360	400
		Endpoint	65	190	90	390*	406
	417.304-054-018	Baseline	81	160	100	330	383
		Endpoint	55	170	100	440**	421*
	417.304-056-010	Baseline	75	130	100	350	391
		Endpoint	66	130	100	400*	420

* = increases ≥ 30 - < 60 and ** = increases ≥ 60

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Long-term Study (105.303)

Patient No.	Treatment Group	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
105.303-007-202	Carbatrol	Baseline	78	170	90	380	433
		Endpoint	73	180	90	410*	452
105.303-015-002	Carbatrol	Baseline	61	180	80	360	363
		Endpoint	70	160	100	390*	421*
105.303-017-014	Carbatrol	Baseline	92	180	100	320	396
		Endpoint	70	190	90	360*	389
105.303-026-001	Carbatrol	Baseline	115	154	81	327	453
		Endpoint	86	170	90	370*	443
105.303-028-003	Carbatrol	Baseline	75	160	100	380	425
		Endpoint	58	150	90	410*	403
105.303-028-005	Carbatrol	Baseline	66	180	100	350	367
		Endpoint	61	190	100	380*	383
105.303-029-007	Carbatrol	Baseline	70	150	90	350	378
		Endpoint	83	160	100	370	435*
105.303-030-001	Carbatrol	Baseline	66	170	100	330	346
		Endpoint	53	170	100	360*	338
105.303-030-003	Carbatrol	Baseline	68	170	100	340	362
		Endpoint	68	160	90	380*	405*
105.303-030-010	Carbatrol	Baseline	45	200	100	440	381
		Endpoint	67	180	90	400	423*
105.303-030-013	Carbatrol	Baseline	78	160	100	350	399
		Endpoint	66	200	100	380*	399

* = increases ≥ 30 - < 60 and ** = increases ≥ 60 (Continued)

List of Subjects with increases ≥ 30 of QT Interval or QTc Bazett in Phase 3 Long-term Study (105.303) - Continued

Patient No.	Treatment Group	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
105.303-030-021	Carbatrol	Baseline Endpoint	67 80	140 160	100 90	370 380	391 439*
105.303-030-202	Carbatrol	Baseline Endpoint	64 69	150 160	100 90	380 400	392 429*
105.303-030-204	Carbatrol	Baseline Endpoint	60 50	180 210	90 100	370 410*	370 374
105.303-030-206	Carbatrol	Baseline Endpoint	56 50	180 170	90 100	350 410**	338 374*
105.303-030-212	Carbatrol	Baseline Endpoint	61 61	160 160	90 90	400 430*	403 434*
105.303-034-001	Carbatrol	Baseline Endpoint	75 71	140 190	90 100	350 390*	391 424*
105.303-034-005	Carbatrol	Baseline Endpoint	60 73	160 190	90 100	360 360	360 397*
105.303-035-201	Carbatrol	Baseline Endpoint	85 62	160 170	80 90	330 380*	393 386
105.303-036-201	Carbatrol	Baseline Endpoint	70 83	150 160	130 150	380 390	410 459*

* = increases ≥ 30 - < 60 and ** = increases ≥ 60

MEETING MINUTES
IND 59,050
30-Day SRD Meeting

Meeting Date: October 22, 1999 **Time:** 10:00 a.m. **Location:** WOCII 4037
Sponsor: Shire Laboratories
SRD Date: October 29, 1999
Drug: Carbatrol® (carbamazepine extended release capsules)
Indication: Acute mania due to bipolar disorder
Meeting Chair: R. Katz, MD **Meeting Recorder:** D. Bates, PhD
Participants: R. Katz, MD; T. Laughren, MD; G. Fitzgerald, PhD; E. Fisher, PhD; I. Mahmood PhD; V. Tammara, PhD; D. Bates, PhD

Background: The subject IND is for the study of carbamazepine extended release capsules in acute mania associated with bipolar disorder.

Recommendations: Chemistry: Chemistry comments were conveyed to Project Manager prior to meeting. There are no CMC issues.

Pharmacology: No pharm/tox issues, study may proceed.

Clinical: No significant clinical issues. The sponsor will need to conduct drug interaction studies, at a minimum to address the potential for interaction with lithium and with antidepressants which may be used concomitantly in this indication. The sponsor has also requested clarification on the number and design of studies needed to support an efficacy supplement in bipolar disorder. The Division's feedback on this issue will be included in our Safe to Proceed letter to the sponsor.

Biopharmaceutics: The proposed study does not include PK monitoring, although blood levels of drug are being determined. The sponsor has confirmed that this is being done to assure that blood levels for patients in this study do not exceed current recommendations.

DECISION: Study may proceed, sponsor to be notified by RPM

ACTION: Sponsor was contacted by telephone subsequent to meeting and informed that study may proceed.

D. Bates, Ph.D., RPM

T. Laughren, M.D.,
Team Leader, Psychiatric Drug Products
Group

30-DAY SRD Meeting Minutes

IND 59,050

Page 2

cc: Original IND 59,050

HFD-120/Division File

HFD-120/Katz

 /Laughren/Hearst

 /Fitzgerald/Fisher

 /Bates

HFD-810/Seevers

HFD-860/Tammara/Mahmood

pathname: d:\...\inds\59050\30daysrd.mm.doc

MEETING MINUTES

IND MAY PROCEED (IND 59,050)

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Friday, October 22, 2004 2:58 PM
To: 'Bates, Doris J'; Levin, Robert; Mota, Linda
Subject: RE: NDA 21-710: Questions, Clinical Reviewer



response 1 to
'1 oct question..

Good afternoon,

Attached is the data requested for question 1. A hard copy will be sent to you on Monday. The remaining information will be forwarded to you on Monday.

I apologize for the delay.

Feel free to contact me at your earliest convenience if you need anything.

<<response 1 to 01 oct question.doc>>

Kind regards

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Friday, October 01, 2004 10:22 AM
To: Lomri, Zohra
Cc: Bates, Doris J; Levin, Robert
Subject: RE: NDA 20-712: Questions, Clinical Reviewer

Good morning Zohra:

Our clinical reviewer would like to request a few more items of information:

1. Please provide the mean and median doses used in the controlled studies.
2. Please provide outlier analyses for the particular ECG parameters (QT, QTcB, QRS, etc.).
3. Please provide documents pertaining to financial disclosure (or direct us to where we might find it in the current submission).

I am including our reviewer as a CC recipient on this e-mail. You may wish

to include him as a CC recipient on your reply, to speed his receipt of the information if I am out of the office or in meetings when the information arrives. Any new information submitted in response should also be submitted to the NDA in the format appropriate to its section, but we can work with information sent by e-mail before the official submission arrives.

Thanks as always,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Please provide the mean and median doses used in the controlled studies.

Table 1 presents summary statistics for the final daily Carbatrol dose taken by subjects during controlled studies (Protocols 105.301, 105.302, and 417.304). Subjects randomized to receive placebo were excluded from this analysis.

Subjects in the combined controlled protocols took a final mean Carbatrol dose of 853.4 mg and a median dose of 800mg. Subjects in Protocol 105.301 took a final mean daily dose of 952.5mg and a median dose of 800mg. Subjects in Protocol 105.302 took a final mean daily dose of 1050.0mg and a median dose of 1100mg. Subjects in Protocol 417.304 took a final mean daily dose of 726.2mg and a median dose of 600mg.

Table 1: Summary of Final Daily Carbatrol Dose Taken During Controlled Phase III Studies	
	Final Daily Carbatrol Dose (mg)
Combined Controlled Protocols (105.301, 105.302, 417.304) N Mean (SD) Min, Max Median	251 853.4 (435.82) 200, 1600 800
Protocol 105.301 N Mean (SD) Min, Max Median	101 952.5 (433.73) 200, 1600 800
Protocol 105.302 N Mean (SD) Min, Max Median	28 1050.0 (440.96) 200, 1600 1100
Protocol 417.304 N Mean (SD) Min, Max Median	122 726.2 (400.17) 200, 1600 600

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, October 21, 2004 10:03 AM
To: Bates, Doris J
Subject: FW: New Meeting Request Received for N 21710 (Meeting ID :14344)

Meeting was placed on calendar on 20 Oct 2004 and this email documents that fact for IMTS.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

-----Original Message-----

From: IMTS@CDER.FDA.GOV [mailto:IMTS@CDER.FDA.GOV]
Sent: None
To: BATESD@CDER.FDA.GOV
Subject: New Meeting Request Received for N 21710 (Meeting ID :14344)

A new meeting request has been received on 20-OCT-2004 for N 21710. The goal date for responding to the request is 03-NOV-2004.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

10/21/04 10:08:21 AM

Type A meeting, granted and placed on calendar on
date of request.

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Wednesday, October 20, 2004 11:46 AM
To: 'batesd@cder.fda.gov'
Cc: Mota, Linda
Subject: NDA 21-710 meeting/teleconference request for tradename



SPD417
Meeting Request 14-

Good morning Doris,

As agreed previously, I am including an electronic copy of a meeting/teleconference. A hard copy of this request is also being sent to you today.

The briefing packet will be sent via email and regular mail on Friday October 20th, 2004.

IF you need additional information/clarifications, feel free to contact me at your earliest convenience.

Kind Regards

Zohra Lomri
Sr. Manager, Regulatory Affairs
Tel (484) 595 - 8364
Fax (484) 595 - 8156
email zlomri@us.shire.com

<<SPD417 Meeting Request 14-Oct-04.doc>>

SPD417 MEETING/TELECONFERENCE REQUEST

1. PRODUCT NAME AND APPLICATION NUMBER

SPD417 carbamazepine extended-release capsule

NDA 21-710 (IND 59,050)

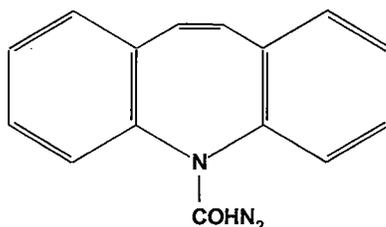
2. CHEMICAL NAME AND STRUCTURE

2.1 Names

Carbamazepine, USP is named in the United States Pharmacopoeia (USP) as 5H-Dibenz[b,f]azepine-5-carboxamide, while other common names for this compound are 5-Carbamoyl-5H-dibenz[b,f]azepine and 2,3:6,7-Dibenzapine-1-carboxylic acid, amide (Merck Index). The Chemical Abstract Service (CAS) number is [298-64-4].

2.2 Formulae

Carbamazepine is an iminostilbene derivative with the empirical formula $C_{15}H_{12}N_2O$. According to the current USP 23/NF 18 it has a molecular weight of 236.27. The structure of carbamazepine is shown below.



Carbamazepine
(5H-Dibenz[b,f]azepine-5-carboxamide)

3. PROPOSED INDICATION

SPD417 is intended for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

4. TYPE OF MEETING BEING REQUESTED

Per *Guidance for Industry: Formal Meetings with Sponsors and Applicants of PDUFA Products*, a **Type A meeting** is requested to discuss the written recommendation presented by the Agency with regard to the dual trade name proposal.

5. PURPOSE OF THE MEETING

Shire recognizes and appreciates the Agency's concern regarding the risk of dual prescribing and prescription errors associated with our proposal for a separate trade name. Shire will present an alternative risk management and communication strategy to minimize the risk associated with dual prescribing of carbamazepine-containing products including our marketed and proposed brands. We will outline the advantages of adopting our risk management plan over prohibiting a separate trade name for the bipolar indication.

6. SPECIFIC OBJECTIVES AND OUTCOMES OF THE MEETING

Shire would like an opportunity to outline our risk management plan, examine other risk management strategies the Agency would like to see implemented if any, and consider alternate proprietary name(s) for SPD417.

7. PROPOSED MEETING AGENDA

Introduction	Zohra Lomri	5 minutes
Discussions	All	50 minutes
Conclusions	Zohra Lomri	5 minutes

8. PROPOSED ATTENDEE LIST

While we have not yet finalized the list of participants, the tentative attendee list is as follows:

Jeffrey Freid, MD	Senior Director, US Pharmacovigilance
Rick Lilley, Ph. D	Senior Vice President, Regulatory Affairs
Zohra Lomri, MS	Senior Manager, Regulatory Affairs
Eliseo Salinas, MD	Executive Vice President, Global R&D
Timothy Whitaker, MD	Vice President, Global Clinical Medicine
Lisa Wittmer, Ph.D.	Director, Regulatory Affairs

9. DRAFT LIST OF QUESTIONS

Question 1

Does the Agency agree that a risk management/risk communication plan is an acceptable alternative strategy to that recommended by the Division (opposing second brand name)?

Question 2

Is Shire's risk management/risk communication plan acceptable and does the Agency have other risk management strategies to suggest.

Question 3

If the answer to Question 1 is "no", will the Agency elaborate on why a risk management plan such as the one Shire has proposed does not more adequately address the Agency's concerns than use of Carbatrol brand name, particularly when there already exists regulatory precedents for approving two brand names for the same active ingredient?

Question 4

Are the alternate proprietary names proposed acceptable?

10. DISCIPLINES OF AGENCY STAFF REQUESTED BY SHIRE TO PARTICIPATE IN THE PROPOSED MEETING

Shire requests that Agency officials representing the following disciplines should participate in the proposed meeting:

- Representatives from the Division of Neuropharmacological Drug Products including Dr. Katz, Division Director
- Representative(s) from the Division of Medication Errors and technical Support.
- Shire understands the potential impact on CDER's policies, consequently we suggest Dr. Temple as an attendee.

11. APPROXIMATE DATE ON WHICH SUPPORTING DOCUMENTATION WILL BE SENT TO THE REVIEW DIVISION

Supporting documentation will be sent to the Review Division two weeks prior to the agreed upon meeting date.

12. SUGGESTED DATES AND TIMES FOR THE MEETING

Shire proposes the following dates and times for the meeting:

- Time: anytime between 8:30 am to 5 pm
- Date: between October 25th, 2004 and November 20th, 2004

Appears This Way
On Original

Shire Pharmaceutical Development Inc
1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404



20 October 2004

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

NDA No: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Amendment to Original New Drug Application:
Type A Meeting Request
Submission No: 008

Dear Dr. Katz:

We refer you to Shire's original New Drug Application (NDA# 21-710) for carbamazepine extended-release capsules, 100mg, 200mg, and 300mg, the subject of IND # 59,050 and to your recommendation regarding the use of an alternate brand name for SPD417 sent on 04 October 2004.

Shire recognizes and appreciates the Agency's concern regarding the risk of dual prescribing and prescription errors associated with our proposal for a separate trade name. Shire hereby requests a Type A Meeting or a teleconference as a forum to discuss an alternative risk management/ communication plan.

If you have any questions regarding this submission, please contact me at (484) 595-8364.

Sincerely,

A handwritten signature in black ink, appearing to read "Zohra E. Lomri".

Zohra Lomri, MS
Senior Manager
Regulatory Affairs

Shire Pharmaceutical Development, Inc.
1801 Research Blvd Rockville MD 20850 USA



Fax

To: Chhagan Tele, Ph.D. **Fax No:** (301) 594 - 2858
Company: Neuropharm Division
From: Zohra Lomri **Fax No:** (484) 595 - 8156
Phone No: (484) 595 - 8364
Date: 21 October 2004 **No. of** (Including cover page)
Pages: 2
Subject: NDA 21-710
Response to question regarding alternate manufacturing sites

The responses are included in the attached.

IF you need further information or clarifications, feel free to contact me at your earliest convenience. A hard copy will also be sent to the Agency shortly

Regards

A handwritten signature in black ink, appearing to read "Zohra Lomri".

Zohra Lomri
Sr. Manager, Regulatory Affairs
Shire Inc.

This message and any accompanying documents are intended only for the use of the individual or entity to which they are addressed and may contain information that is privileged, confidential and exempt from disclosure under applicable law. If the receiver of this message is not the intended recipient or the employee or the agent responsible for delivering the message to the intended recipient, you are hereby warned that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please contact us by telephone so we can arrange for its return. Thank you.

Bates, Doris J

From: Bates, Doris J

Sent: Wednesday, October 13, 2004 5:24 PM

To: Katz, Russell G; Laughren, Thomas P; Oliver, Thomas F; Hoppes, Charles V; Holquist, Carol A; Bates, Doris J

Subject: NDA 21-710: Teleconference with Shire, October 13, 2004.

BACKGROUND:

Shire currently markets controlled-release carbamazepine as Carbatrol for TGN and epilepsy, with a different trade dress. Agency feedback provided to the firm on October 4 (secure e-mail, in DFS) rejects the proposed alternate trademark and presents specific reasoning to support this position.

On October 5, Shire verbally requested a telecon to discuss this feedback with the Division. I then advised Ms. Lomri that the best follow-up would be for the firm to prepare a response to our feedback and submit it as part of their meeting request, so that the basis for further discussion is in place when the request is received. I also assured her that we would respond expeditiously once the request arrives.

TELECONFERENCE:

Ms. Lomri from Shire contacted me this afternoon (October 13) and left a voice mail to inform me that representatives of Shire management wished to have a short teleconference with Dr. Katz and other parties involved in the October 4 Agency recommendation concerning their proposed trademark, next week if possible, without submitting additional documentation first.

Following internal consultation I returned Ms. Lomri's call and explained that the FDA participants would still need some specific information as the basis for meeting, because this is an issue affecting more than one department within the Agency, rather than being a topic that could be discussed and decided within this Division alone.

I explained that our feedback had been cleared through these departments and does represent our current position, so that we would need some specific response to this feedback even to discuss the merits of that position, if this is what is desired.

Ms Lomri then explained that Shire is concerned about the time it will take to hold such a meeting, and I agreed that it would be crucial for us to get some basis for discussion in hand as quickly as possible because there would be two meetings to schedule (counting the internal pre-meeting) and a number of FDA participants' calendars to coordinate. I noted that the firm could request a Type A meeting if they so desired.

Ms Lomri understood the Agency's position, and the teleconference concluded cordially. She will report to her management and contact me regarding next steps.

A copy of this email will be placed in DFS as a memorandum of the telecon.

10/13/2004

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates
10/13/04 05:50:20 PM
CSO

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Wednesday, October 06, 2004 4:56 PM
To: 'Bates, Doris J'
Subject: RE: NDA 21-710 Clinical Question

Thanks Doris,

FYI: we are sending today a letter to withdraw a — manufacturing site from the 21-710 NDA. you should get it in the next couple of days.

Zohra

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Wednesday, October 06, 2004 3:51 PM
To: Lomri, Zohra
Subject: RE: NDA 21-710 Clinical Question

Thank you Zohra, we received the message and the attachment, and I was able to open the attachment without any difficulty.

Best regards,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research*

-----Original Message-----

From: Lomri, Zohra [mailto:ZLomri@us.shire.com]
Sent: Wednesday, October 06, 2004 3:40 PM
To: 'Bates, Doris J'; Levin, Robert
Subject: RE: NDA 21-710 Clinical Question

Good afternoon Doris,

Attached are Shire's responses to requests listed in the below email. As previously agreed, A hard copy is also sent to you.

Regarding Dr. Levin requests of October 1st, please note that a preliminary estimate to address requests 1 and 2 is of several weeks. I will provide you with a more accurate date of delivery as soon as I can.

As usual, feel free to contact me at your earliest convenience should you need additional information/clarifications.

Kind Regards

Zohra Lomri
Sr. Manager, regulatory Affairs

11/28/2004

U.S. Research and Development Inc.
1801 research Boulevard
ph# (484) 595 - 8364
fax# (484) 595 - 8156
zlomri@us.shire.com

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Wednesday, September 22, 2004 4:35 PM
To: Lomri, Zohra
Cc: Bates, Doris J; Levin, Robert
Subject: NDA 21-710 Clinical Question

Good afternoon Zohra:

Our clinical reviewer would like to request the following information: (If it is already in the submission, please let us know where to find it).

- Please provide the Carbatrol exposures in patient years for each of the studies separately.
- Please provide the total lorazepam use in mg for each treatment group (for the 3 acute studies).
- Please specify the criteria for categorizing a subject as lithium-nonresponsive or lithium-intolerant.
- Please provide more details about those discontinuations categorized as "subject choice" and "withdrew consent."

I am experiencing problems with my email, for which I have put in a service call. I believe this request may have been sent to you previously, but I can find no record of my having done so, and I would rather repeat myself than fail to send you a request for information that is key to finishing our review.

Dr. Levin needs this information as soon as possible. A reply by secure email is fine, but you should follow up with a formal submission to the file for the record. Please feel free to reply to Dr. Levin if you respond by e-mail, since I do not know how long my email will continue to function, or when the technician will arrive to help me.

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Wednesday, October 06, 2004 3:40 PM
To: 'Bates, Doris J'; Levin, Robert
Subject: RE: NDA 21-710 Clinical Question

Good afternoon Doris,

Attached are Shire's responses to requests listed in the below email. As previously agreed, A hard copy is also sent to you.

Regarding Dr. Levin requests of October 1st, please note that a preliminary estimate to address requests requests 1 and 2 is of several weeks. I will provide you with a more accurate date of delivery as soon as I can.

As usual, feel free to contact me at your earliest convenience should you need additional information/clarifications.

Kind Regards

Zohra Lomri
Sr. Manager, regulatory Affairs
U.S. Research and Development Inc.
1801 research Boulevard
ph# (484) 595 - 8364
fax# (484) 595 - 8156
zlomri@us.shire.com

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Wednesday, September 22, 2004 4:35 PM
To: Lomri, Zohra
Cc: Bates, Doris J; Levin, Robert
Subject: NDA 21-710 Clinical Question

Good afternoon Zohra:

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- Please specify the criteria for categorizing a subject as lithium-nonresponsive or lithium-intolerant.
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I am experiencing problems with my email, for which I have put in a service call. I believe this request may have been sent to you previously, but I can find no record of my having done so, and I would rather repeat myself than fail to send you a request for information that is key to finishing our review.

Dr. Levin needs this information as soon as possible. A reply by secure email is fine, but you should follow up with a formal submission to the file for the record. Please feel free to reply to Dr. Levin if you respond by e-mail, since I do not know how long my email will continue to function, or when the technician will arrive to help me.

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Comment 1:

Please provide the Carbatrol exposures in patient years for each of the studies separately.

Response:

Duration of Carbatrol exposure in patient years is presented by study and as overall exposure in Table 1 (following page). Overall exposure to Carbatrol in these trials (short & long term combined) was 31.69 patient years. Two hundred and fifty-one (251) patients were exposed to Carbatrol in the short-term trials and 92 patients were exposed to Carbatrol in the long-term trial. The majority of drug exposure, 20.80 patient years, was in the long-term trial. Exposure within the short-term trials accounted for a total of 10.89 years of patient exposure, consisting of 4.03 years in Protocol 105.301, 1.06 years in Protocol 105.302, and 5.79 years in Protocol 417.304.

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On Original*

Table 1: Duration of Subjects Receiving Study Medication According to Daily Dose and Duration of Therapy in Phase 3 Studies

Drug Exposure (Years)	Carbatrol Daily Dose (mg)					Total Cabatrol
	200	400-600	800-1000	1200-1400	1600	
Short Term Study (#105.301)						
N	6	99	90	62	35	101
Mean Years per Subject (SD)	0.00 (0.00)	0.01 (0.01)	0.01 (0.02)	0.01 (0.01)	0.02 (0.02)	0.04 (0.02)
Sum (Person Years)	0.02	1.08	1.35	0.83	0.75	4.03
Short Term Study (#105.302)						
N	1	27	25	21	8	28
Mean Years per Subject (SD)	0.00 (0.00)	0.01 (0.01)	0.02 (0.01)	0.01 (0.01)	0.02 (0.01)	0.04 (0.02)
Sum (Person Years)	0.00	0.30	0.38	0.23	0.15	1.06
Short Term Study (#417.304)						
N	12	120	107	77	47	122
Mean Years per Subject (SD)	0.00 (0.00)	0.01 (0.01)	0.02 (0.02)	0.02 (0.01)	0.02 (0.01)	0.05 (0.02)
Sum (Person Years)	0.04	1.61	1.98	1.21	0.94	5.79
Long-term (#105.303)						
N	1	25	51	35	44	92
Mean Years per Subject (SD)	0.02 (0.00)	0.15 (0.18)	0.14 (0.14)	0.11 (0.13)	0.11 (0.14)	0.23 (0.18)
Sum (Person Years)	0.02	3.81	7.09	3.86	4.81	20.80
Short Term Studies						
N	19	246	222	160	90	251
Mean Years per Subject (SD)	0.00 (0.00)	0.01 (0.01)	0.02 (0.02)	0.01 (0.01)	0.02 (0.01)	0.04 (0.02)
Sum (Person Years)	0.07	2.98	3.71	2.27	1.84	10.89
Short and Long Term Studies						
N	20	259	248	184	124	299
Mean Years per Subject (SD)	0.00 (0.00)	0.03 (0.08)	0.04 (0.09)	0.03 (0.07)	0.05 (0.09)	0.11 (0.14)
Sum (Person Years)	0.09	6.79	10.80	6.13	6.65	31.69

Comment 2:

Please provide the total lorazepam use in mg for each treatment group (for the 3 acute studies).

Response:

Table 2 and Table 3 (following pages) present the total lorazepam dose and total duration of lorazepam use for Protocols 105.301, 105.302, and 417.304.

Data entry guidelines for Protocols 105.301 and 105.302 allowed sites to record drugs that were taken on an 'as needed basis' (i.e. 'PRN'), without clarification of the patient's regular dose. Lorazepam was not provided by the sponsor and no pill counts for lorazepam use were conducted during the study. Consequently, precise dosage of 'PRN' use is not possible. Patients with 'PRN' doses did have start and stop dates for lorazepam use, so duration of exposure can be calculated using data from these patients.

Data entry requirements for Protocol 417.304 specified that all lorazepam use must be listed on the Case Report Form. These records included dose and duration of use. Precise use of lorazepam in this study is available.

Of the 204 subjects randomized into Study #105.301, 141 subjects were prescribed lorazepam. Seventy-two (72) of these subjects had records of dose and frequency in the case report form (CRF): 36 subjects in the Carbatrol treatment group and 36 subjects in the placebo treatment group. Subjects in the Carbatrol treatment group with records of dose and frequency of lorazepam use, took a mean daily dose of 7.76 mg lorazepam. Subjects in the placebo treatment group with records of dose and frequency of lorazepam use took a mean dose of 5.77 mg lorazepam. The remaining 69 patients had PRN dosing records, and were excluded from the calculation of mean dose, however these subjects were included in the calculation of mean duration of use. The mean duration of lorazepam use was 8.22 days in the Carbatrol treatment and 8.78 days in the placebo treatment group.

Of the 59 subjects randomized into Study #105.302, 47 subjects were prescribed lorazepam. Eighteen (18) of these subjects had records of dose and frequency in the CRF: 10 subjects in the Carbatrol treatment group and 8 subjects in the placebo treatment group. Subjects in the Carbatrol treatment group with records of dose and frequency of lorazepam use took a mean dose of 7.35 mg lorazepam. Subjects in the placebo treatment group with records of dose and frequency of lorazepam use took a mean dose of 5.25 mg lorazepam. The remaining 29 patients had PRN dosing records, and were excluded from the calculation of mean dose, however these subjects were included in the calculation of mean duration of use. The mean duration of lorazepam use was 7.78 days in the Carbatrol treatment and 11.33 days in the placebo treatment group.

Of the 239 subjects randomized into Study #417.304, 182 subjects used lorazepam during the trial. All subjects had complete records of dose and duration of treatment. The 90 subjects in the Carbatrol treatment group took a mean daily dose of 6.44 mg

lorazepam for a mean duration of 7.9 days. The 92 subjects in the placebo group took a mean daily dose of 7.69 mg lorazepam for a mean duration 9.02 days.

Patients in the Carbatrol and placebo groups of SPD417.304 used a total of 4578.84 mg and 6381.47 mg lorazepam, respectively, calculated by multiplying the mean daily lorazepam dose (mg/day) by the mean duration of use (days) and the number of patients reporting use.

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Table 2: Summary of Total Lorazepam Dose Taken During Double-Blind Treatment Period

Total Lorazepam (mg)	Treatment Group		Total
	Carbatrol	Placebo	
Study #105.301			
N ^a	36	36	72
Mean (SD)	7.76 (8.88)	5.77 (5.42)	6.77 (7.37)
Median	3.80	4.00	4.00
Min, Max	1, 40	1, 27	1, 40
Sum	279.35	207.75	487.10
No. of Subjects with Only PRN Prescribed	30	28	58
No. of Subjects with PRN and dose Prescribed	6	5	11
Study #105.302			
N ^a	10	8	18
Mean (SD)	7.35 (5.46)	5.25 (3.88)	6.42 (4.81)
Median	7.25	5.50	6.00
Min, Max	1, 18	2, 14	1, 18
Sum	73.50	42.00	115.50
No. of Subjects with Only PRN Prescribed	13	15	28
No. of Subjects with PRN and dose Prescribed	0	1	1
Study #417.304			
N	90	92	182
Mean (SD)	6.44 (4.80)	7.69 (5.79)	7.07 (5.34)
Median	6.00	6.00	6.00
Min, Max	1, 22	1, 25	1, 25
Sum	580.00	707.50	1287.50
No. of Subjects with Only PRN Prescribed	0	0	0
No. of Subjects with PRN and dose Prescribed	0	0	0

a: Includes only those patients who had complete Lorazepam dose information during double-blind period.

Table 3: Summary of Total Lorazepam Use in Duration Taken During Double-Blind Treatment Period			
Total Duration of Lorazepam Use (days)	Treatment Group		Total
	Carbatrol	Placebo	
Study #105.301			
N	72	69	141
Mean (SD)	8.22 (5.64)	8.78 (6.46)	8.50 (6.04)
Median	6.00	7.00	6.00
Min, Max	1, 26	1, 26	1, 26
Sum	592.00	606.00	1198.00
Study #105.302			
N	23	24	47
Mean (SD)	7.78 (6.61)	11.33 (6.63)	9.60 (6.79)
Median	6.00	11.00	7.00
Min, Max	1, 24	3, 28	1, 28
Sum	179.00	272.00	451.00
Study #417.304			
N	90	92	182
Mean (SD)	7.90 (5.33)	9.02 (4.64)	8.47 (5.01)
Median	6.50	8.50	8.00
Min, Max	1, 31	1, 21	1, 31
Sum	711.00	830.00	1541.00

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Comment 3:

Please specify the criteria for categorizing a subject as lithium-nonresponsive or lithium-intolerant

Response:

Protocol 105.302 inclusion criteria specified that patients must have 'a history of lack of tolerance or lack of therapeutic response to lithium' to qualify for enrollment. Investigators were asked to use clinical judgment to determine if a patient met either of these criteria.

Communications to the site, provided by the CRO medical monitor, were that patients may be considered lithium-nonresponsive following trial with an adequate dose of lithium for an adequate duration of time without adequate therapeutic response.

Comment 4:

Please provide more details about those discontinuations categorized as "subject choice" and "withdrew consent."

Response:

For the purpose of the Carbatrol Bipolar trials (105.301, 105.302, 105.303, and 417.304) "subject choice" and "withdrew consent" were interchangeable terms.

Data handling guidelines specified that comments must be provided if "adverse event", "protocol violation", or "other" was chosen as the reason for discontinuation. Sites were not required to include any comments or additional details for patients who discontinued due to "subject choice" or "withdrew consent".

Steps were taken during data review to ensure subjects with adverse experiences (AEs) leading to discontinuation were not captured as "subject choice" or "withdrew consent". Any AEs with an action taken listed as "study drug discontinued" were cross checked with responses on the End of Study (EOS) CRF page. If the EOS page stated that subject withdrew due to "subject choice", then a query was sent to the site to ensure an AE was not the cause for subject discontinuation.

Discontinuations due to lack of efficacy were not investigated during data review. It was left to the investigator to determine whether the subject withdrew due to lack of therapeutic benefit. Furthermore, it was at the discretion of the investigator to withdraw a subject should the investigator feel the subject was not receiving any therapeutic benefit. Such terminations were captured as "lack of efficacy".

Shire Pharmaceutical Development Inc
1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404



06 October 2004

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

NDA# 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Amendment to Original New Drug Application
Responses to clinical review comments of 22 September 2004
Submission No: 007

Dear Dr. Katz,

We refer you to Shire's original New Drug Application (NDA# 21-710) for carbamazepine extended-release capsules, 100mg, 200mg, and 300mg, the subject of IND #59,050.

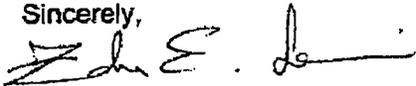
On 22 September 2004, Dr. Bates forwarded via email the following comments from Dr. Levin (clinical reviewer).

1. Please provide the Carbatrol exposures in patient years for each of the studies separately.
2. Please provide the total lorazepam use in mg for each treatment group (for the 3 acute studies).
3. Please specify the criteria for categorizing a subject as lithium-nonresponsive or lithium-intolerant.
4. Please provide more details about those discontinuations categorized as "subject choice" and withdrew consent."

The responses to the comments are included in this correspondence. Please note this information has been forwarded to Dr. Bates and Dr. Levin via secure email.

If you have any questions regarding this submission, please contact me at
(484) 594 - 8364

Sincerely,

A handwritten signature in black ink, appearing to read 'Zohra Lomri', written over a horizontal line.

Zohra Lomri
Senior Manager
Regulatory Affairs

Bates, Doris J

From: Bates, Doris J
Sent: Tuesday, October 05, 2004 3:25 PM
To: Bates, Doris J
Subject: Telecon Memo - N 21710 - Tcon regarding Trademark

Ms. Lomri from Shire contacted me this morning at ca. 11:50 a.m. to inform me that the firm had received and discussed yesterday's Agency feedback (precleared secure e-mail, in DFS) concerning their proposed trademark, [] for controlled-release carbamazepine in mania.

Shire currently markets controlled-release carbamazepine as Carbatrol for TGN and epilepsy, with a different trade dress. The Agency feedback provided yesterday rejects the proposed alternate trademark and presents specific reasoning to support this position.

Shire is interested in a meeting (telecon) to discuss this feedback with the Division. I advised Ms. Lomri that the best follow-up would be for the firm to prepare a response to our feedback and submit it as part of the meeting request, so that the basis for further discussion is in place when the request is received. I also assured her that we would respond expeditiously once the request arrives.

The teleconference concluded cordially.

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research*

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this page is the manifestation of the electronic signature.**

/s/

Doris Bates
10/5/04 04:41:06 PM
CSO

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

2. Dual Tradenames for the Same Active Ingredient

The applicant currently proposes to market their Carbamazepine Extended-release Capsules product for a new indication, acute mania due to bipolar disorder, under the proprietary name, Carbatrol® (Carbamazepine Extended-release Capsules) has been marketed since its approval on September 30, 1997, for use in epilepsy and trigeminal neuralgia (NDA 20-712). The applicant has provided the following justification for the proposal of a new product name with separate labeling:

Reason 1

These indications (epilepsy/trigeminal neuralgia and bipolar disorder) are distinct and require different dosing schedules. A rapidly escalating daily dosing schedule not studied in other patient populations is specific for the bipolar patient population and different trade dress, trade name and prescribing information will reinforce appropriate use of Carbatrol in the patient populations with epilepsy and trigeminal neuralgia and of Carbatrol in patients with bipolar disorder.

FDA Response

FDA acknowledges that the indications, epilepsy/trigeminal neuralgia and bipolar disorder, are distinct and require different dosing schedules. However, many products exist that have more than one indication and separate dosing regimens, yet the same proprietary name. FDA does not believe that this fact in itself necessitates the creation of a separate product with a separate proprietary name. If that were the case, there would already be two carbamazepine products, one for epilepsy and one for trigeminal neuralgia, since these indications and dosage recommendations are distinct. Additionally, the applicant gives no justification nor provides evidence for how different trade dress will affect the appropriate use of Carbatrol versus Carbatrol. In fact, FDA can find no evidence of confusion between the separate patient populations with epilepsy and trigeminal neuralgia for the existing Carbatrol product.

Reason 2

Product presentation plays a role in treatment compliance, therefore the original teal and gray/black Carbatrol capsules have been re-colored in trade dress more appropriate for the bipolar population in yellow and green/blue hues.

FDA Response

FDA requests the applicant to present evidence to substantiate the assertion that the color of the capsules will affect the proper use of the product, i.e., that a capsule with yellow and green/blue hues would be more appropriate for the bipolar population than a teal and gray/black capsule.

Reason 3

The risk of double prescribing is very low as only 1% of patients being treated for epilepsy have a co-diagnosis of bipolar mood disorder (IMS Health's National Disease and Therapeutic Index (NDTI) included in appendix). Additionally, the proposed package insert (see Precautions) includes a statement reinforcing the fact that Carbatrol should not be used in combination of other drug products containing carbamazepine.

FDA Response

A. Not only does the applicant admit to the increased risk (although low) of double prescribing between patients being treated for epilepsy and bipolar mood disorder, but the proposal fails to assess the additional risks associated with treatment of trigeminal neuralgia and any off labeled use of Carbatrol. An overview of concerns regarding dual proprietary names for the same active ingredient follows.

The Agency has evidence that the same active ingredient has been coprescribed in events involving different proprietary names from the same manufacturer. Depending on the safety profile of the product, the potential for harm exists when this occurs. Safety concerns may arise, for example, in several situations:

- ✘ Practitioners and patients may not realize that two drug products with different names contain the same active ingredient. This could lead to prescribing the same active ingredient twice if a patient sees different practitioners, or if neither the patient nor the practitioner recognizes the presence of the same active ingredient in both products.
- ✘ A patient who is allergic to or intolerant of an active ingredient in a product might unknowingly take the active ingredient, thinking that because this product has different proprietary name, it doesn't contain the active ingredient.

B. FDA is particularly concerned that two health care professionals may prescribe the same active ingredient (with different proprietary names) to a single patient for two different indications, thereby exposing the patient to an increased dose of the medication. In this case, a patient could be seen by a psychologist for bipolar disorder and receive a prescription for then be seen by medical doctor or neurologist for problems with seizure disorder or trigeminal neuralgia and receive a separate prescription for Carbatrol. Availability of generic products for and Carbatrol may compound confusion since a patient could be on Carbatrol, and carbamazepine. The patient and doctors may never realize that the patient is receiving the same medication from two sources.

Dual prescribing is a concern as and Carbatrol are drugs which are both indicated for long-term administration. FDA is concerned about the chronic use of and Carbatrol together since carbamazepine appears to have dose-related adverse effects, including dizziness, drowsiness, unsteadiness, nausea and vomiting.

Additionally, there have been reports of transient or persistent decreased platelet or white blood cell count in association with the use of carbamazepine. Removal of the association of with its seizure indication could also increase the likelihood of its administration with the Trileptal (oxcarbazepine), a carbamazepine derived antiepileptic. FDA believes that the concurrent administration of Carbatrol and Trileptal would be less likely than and Trileptal since Carbatrol and Trileptal have product recognition as anti-epileptic carbamazepines.

As part of the risk analysis regarding dual tradenames for carbamazepine products, FDA sought to determine any existing potential for confusion between carbamazepine containing products. Reports of confusion between the applicant's existing carbamazepine product, Carbatrol and other carbamazepine products were of particular interest. FDA conducted a search of the FDA Adverse Event Reporting System (AERS) using MedDRA Preferred Terms (PTs), "Medication

Error", "Accidental Overdose", "Overdose", "Pharmaceutical Product Complaint", and "Treatment Non-Compliance", and the drug name, "Carbatrol%", were used to perform the search. These searches yielded two reports of confusion between Carbatrol and other carbamazepine containing products. In one instance, Carbatrol and Tegretol were taken together resulting in carbamazepine toxicity. The post-marketing reports of confusion between Carbatrol and Tegretol, increases FDA's level of concern that the introduction of another carbamazepine product, with different name and separate indication of use, into the marketplace will increase the duplicate carbamazepine use.

We believe there are no public health risks or stigmas associated with the use of one proprietary name for this drug product. Nor has the applicant presented public health risks or stigmas associated with the use of one proprietary name for this drug product. Therefore, the safe use of this product is best managed under one proprietary name.

3. FDA acknowledges results of a study conducted by [redacted] [redacted] dated January 22, 2004). However, the information presented in support of the name failed to provide persuasive evidence on the acceptability of the name.

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/s/

Doris Bates

10/4/04 01:28:51 PM

CSO

sent to firm on date checked in to DFS.

See email for transmission time.

Bates, Doris J

From: Bates, Doris J
Sent: Monday, October 04, 2004 1:16 PM
To: 'Lomri, Zohra'
Cc: Bates, Doris J
Subject: RE: NDA 20-712: Feedback Concerning Proposed Alternate Trademark, []



COMMENTS
ADEMARK.pdf

Dear Ms. Lomri:

We have completed our review of your proposed trademark and trade dress [] with alternate capsule shell colors and branding) for carbamazepine in the treatment of bipolar disorder.

At this time, we are not prepared to approve your proposed alternate trademark and trade dress. Our reasoning is provided in the attached .pdf file. We would instead, at the time of final approval of this application, propose to approve your existing product Carbatrol for this indication. Please note that this feedback does not imply a specific outcome for our ongoing efficacy and safety reviews at this time; our comment relates only to the proposed alternate trademark and trade dress.

I will be contacting you by phone to confirm receipt of this message. This e-mail transmission can be considered official Agency correspondence.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Friday, October 01, 2004 3:09 PM
To: 'Bates, Doris J'
Cc: Levin, Robert
Subject: RE: NDA 20-712: Questions, Clinical Reviewer



financial
disclosure.pdf (1 M)

Hello,

AS discussed earlier, I am providing with the answer to item# 3: "Please provide documents pertaining to financial disclosure (or direct us to where we might find it in the current submission)."

The financial Disclosure form and attachment are included in Volume, Module 1, Tab: Financial Disclosure. A copy from the NDA is included for your convenience. Should you require additional information, or if I misunderstood your request, please contact me at your earliest convenience. The responses to item#1 and #2 will be provided Monday.

Please note a hard copy will be provided with the responses to item#1 and #2

Kind Regards

Zohra Lomri
Sr. Manager, regulatory Affairs
U.S. Research and Development Inc.
1801 research Boulevard
ph# (484) 595 - 8364
fax# (484) 595 - 8156
zlomri@us.shire.com <mailto:zlomri@us.shire.com>

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Friday, October 01, 2004 10:22 AM
To: Lomri, Zohra
Cc: Bates, Doris J; Levin, Robert
Subject: RE: NDA 20-712: Questions, Clinical Reviewer

Good morning Zohra:

Our clinical reviewer would like to request a few more items of information:

1. Please provide the mean and median doses used in the controlled studies.
2. Please provide outlier analyses for the particular ECG parameters (QT,

QTcB, QRS, etc.). 3. Please provide documents pertaining to financial disclosure (or direct us to where we might find it in the current submission).

I am including our reviewer as a CC recipient on this e-mail. You may wish to include him as a CC recipient on your reply, to speed his receipt of the information if I am out of the office or in meetings when the information arrives. Any new information submitted in response should also be submitted to the NDA in the format appropriate to its section, but we can work with information sent by e-mail before the official submission arrives.

Thanks as always,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Wednesday, September 22, 2004 4:43 PM
To: 'Bates, Doris J'
Cc: Mota, Linda
Subject: RE: NDA 21-710 Clinical Question

Hello Doris, I have forwarded your request to my team. I wanted to acknowledge receipt of your email.

Regards

Zohra Lomri
Sr. Manager, regulatory Affairs
U.S. Research and Development Inc.
1801 research Boulevard
ph# (484) 595 - 8364
fax# (484) 595 - 8156
zlomri@us.shire.com

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Wednesday, September 22, 2004 4:35 PM
To: Lomri, Zohra
Cc: Bates, Doris J; Levin, Robert
Subject: NDA 21-710 Clinical Question

Good afternoon Zohra:

Our clinical reviewer would like to request the following information: (If it is already in the submission, please let us know where to find it).

- Please provide the Carbatrol exposures in patient years for each of the studies separately.
- Please provide the total lorazepam use in mg for each treatment group (for the 3 acute studies).
- Please specify the criteria for categorizing a subject as lithium-nonresponsive or lithium-intolerant.
- Please provide more details about those discontinuations categorized as "subject choice" and "withdrew consent."

I am experiencing problems with my email, for which I have put in a service call. I believe this request may have been sent to you previously, but I can find no record of my having done so, and I would rather repeat myself than fail to send you a request for information that is key to finishing our review.

Dr. Levin needs this information as soon as possible. A reply by secure email is fine, but you should follow up with a formal submission to the file for the record. Please feel free to reply to Dr. Levin if you respond by e-mail, since I do not know how long my email will continue to function, or when the technician will arrive to help me.

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products

Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Rajinder Shiwach, M.D.
2000 N. Old Hickory Trail
DeSoto, Texas 75115

AUG 12 2004

Dear Dr. Shiwach:

Between June 1 and 7, 2004, Mr. Marc R. Dickens, representing the United States (U.S.) Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations:

Protocol 105.301 entitled "A Three-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Safety and Efficacy Study of Extended Release Carbamazepine in Patients with Bipolar Disorder"; and

Protocol 417.304 entitled "a Phase III, Three-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Safety and Efficacy Study of Extended Release Carbamazepine in Patients with Bipolar Disorder" of the investigational drug carbamazepine (Carbatrol), performed for Shire.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Dickens presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your letter dated June 15, 2004, and wish to emphasize the following:

1. You did not adhere to the investigational plan (21 CFR 312.60).

The protocol specified "a history of alcohol or substance abuse or dependence (except caffeine or nicotine) within 1 month of the start of the double-blind treatment (as defined in the DSM-IV)" as one of the exclusionary criteria for enrollment in the study. You enrolled the following subjects who met this exclusionary criterion.

Protocol 105.301

Subject 05: cocaine and cannabis abuse

Subject 11: opioid dependence

Subject 19: alcohol, cocaine and cannabis abuse

Subject 21: cannabis abuse

Protocol 417.304

Subject 12: cannabis abuse

2. You did not promptly report all unanticipated problems involving risk to human subjects to the IRB (21 CFR 312.66).

You submitted serious adverse event (SAE) reports to the IRB for subject 25 enrolled in protocol 105.301 three years after the event occurred. This subject was hospitalized on [] for exacerbation of symptoms of mania. You did not report this serious adverse event to the IRB until 4/26/04.

3. You did not maintain adequate and accurate case histories that record all observations and data pertinent to the investigation [21 CFR 312.62(b)].

For three subjects (8, 10 and 19), vital sign measurements were not done at their baseline study visits for protocol 105.301. Subject 21 did not have the vital sign measurements at screening.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Dickens during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,



Joseph Salewski

Acting Branch Chief

Good Clinical Practice Branch I, HFD-46

Division of Scientific Investigations

Office of Medical Policy

Center for Drug Evaluation and Research

7520 Standish Place, Room 125

Rockville, MD 20855

FEI: . .

Field Classification: VAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response received and reviewed
- 4)OAI

Deficiencies noted:

- failure to adhere to protocol (05)
- inadequate and inaccurate records(06)
- failure to notify IRB of changes, failure to submit progress reports (15)

cc:

HFA-224
HFD-120 Doc.Rm. NDA 21-710
HFD-120 Review Div.Dir. Katz
HFD-120 MO Levin
HFD-120 PM D. Bates
HFD-46 c/r/s GCP File #11226
HFD-46 MO Khin
HFR-SW150 DIB Thornburg
HFR-SW1540 BIMO Martinez
HFR-SW100 Investigator Dickens
GCF-1 Seth Ray

r/d:NK(7/29/04)

reviewed:JPS(8/12/04)

f/t:8/12/04

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DSI Reviewer Note to Rev. Div. Clinical Reviewer

The clinical studies (protocol 105.301 and 417.304) were conducted in Terrell State Hospital, a state run inpatient psychiatric hospital. Dr. Shiwach is no longer employed by Terrell State Hospital as the Research Department was closed in May 2003 due to the State Funding issues. Currently, he works at the Cedars Hospital, DeSoto, Texas.

For protocol 105.301, 26 subjects were enrolled in the study. 16 subjects discontinued and 10 subjects completed the study. For protocol 417.304, 17 subjects were enrolled in the study, 11 subjects discontinued and 6 subjects completed.

Based on the information provided in the EIR, the FDA investigator verified the presence of signed informed consent for each subject. The FDA investigator compared the data recorded in the source documents with the data recorded in the CRF. A Form FDA-483 was issued at the end of inspection. Dr. Shiwach responded to the FDA-483 in a letter dated June 15, 2004.

Inspectional findings:

The protocol specified “a history of alcohol or substance abuse or dependence (except caffeine or nicotine) within 1 month of the start of the double-blind treatment (as defined in the DSM-IV)” as one of the exclusionary criteria for enrollment in the study. Dr. Shiwach enrolled the following subjects who met this exclusionary criterion.

Protocol 105.301

Subject 05: cocaine and cannabis abuse; positive tox screen for cocaine

Subject 11: opioid dependence; opioid overdose and withdrawal within 1 month of double blind treatment

Subject 19: alcohol, cocaine and cannabis abuse

Subject 21: cannabis abuse

Protocol 417.304

Subject 12: cannabis abuse; positive tox screen for cannabis

For three subjects (8, 10 and 19), vital sign measurements were not done at their baseline study visits for protocol 105.301. Subject 21 did not have the vital sign measurements at screening.

The review division should note above protocol violation: enrollment of 5 subjects who met the exclusionary criteria for substance abuse or dependence within 1 month of the double-blind treatment. The review division should consider any impact of such finding on study data. Otherwise, data appear acceptable.

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/s/

Joseph Salewski
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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Shire Pharmaceutical Development Inc
1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

DUPLICATE

15 July 2004

RECEIVED

JUL 16 2004

DDR-120 / CDER

The Shire logo consists of a stylized, curved line above the word "Shire" in a bold, sans-serif font.

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Center for Drug Evaluation and Research
Woodmont II Building
1451 Rockville Pike
Rockville, Maryland 20852

NDA#: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: General Correspondence (Reference Article Translations)
Submission No.: 005

NEW CORRESPONDENCE

N/C

Dear Dr. Katz:

Reference is made to a New Drug Application, NDA 21-710, for carbamazepine extended-release capsules submitted on 13 February 2004 as Submission No. 000.

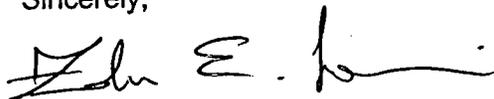
Please find enclosed English translations to the reference articles provided in Module 5, Volume 39-41, Literature References. The following articles were initially provided in a foreign language format; the translation was inadvertently omitted in the original NDA submission:

- DeBoever M, et al. Intolerance a la carbamazepine mimant une mononucleuse infectieuse: a propos de trios cas. Therapie, 1999; 54: 489-491. Module 5, Volume 39, tab identifieur DeBoever.
- Elstner S and Sperling W. Das Carbamazepin Hypersensitivitats-Syndrom. Fortschr Neurol Psychiat, 2000; 68: 188-192. Module 5, Volume 39, tab identifieur Elstner.
- Eren I and Civi I. Bipolar Bozuklukta Karbamazepin Kullanimina Bagli Gelisen Osteopeni: Bir Olgu Sunumu. Klinik Psikofarmakoloji Bulteni, Cilt: 12, Sayi: 3, 2002. Module 5, Volume 39, tab identifieur Eren.
- Skorik AI. Plasma Lithium Level Under Combined Lithium Carbonate/Carbamazepine Therapy. Pharmacology and Toxicology, 1991; 54(4): 57-59. Module 5, Volume 41, tab identifieur Skorik.
- Soucek K. Overcoming Resistance to Lithium Prophylaxis. Ceskoslovenska psychiatrie, 1991; 87(2): 73-75. Module 5, Volume 41, tab identifieur Soucek.

Page 2
NDA 21-710
Submission No. 005

If you have any questions regarding this submission, please contact me at (240) 453 – 6447.

Sincerely,

A handwritten signature in black ink, appearing to read "Zohra E. Lomri". The signature is fluid and cursive, with a long horizontal stroke at the end.

Zohra Lomri
Senior Manager
Regulatory Affairs

Enclosures

Bates, Doris J

From: Khin, Ni Aye
Sent: Friday, April 02, 2004 10:15 AM
To: Bates, Doris J; Siddiqui, Ohidul I; Levin, Robert
Subject: RE: NDA 21-710 Carbatrol

Hi Doris,

You are absolutely right. I just called the sponsor to prepare the site specific information package for the audit of 2 domestic sites (Drs. Lerman and Shiwach). Thanks.

--Ni

-----Original Message-----

From: Bates, Doris J
Sent: Friday, April 02, 2004 10:10 AM
To: Siddiqui, Ohidul I; Khin, Ni Aye; Levin, Robert
Subject: RE: NDA 21-710 Carbatrol

Thanks Ohid! If I understand correctly, this means I do not need to prepare a DSI consult request for this submission to cover any international sites. Ni, please correct me if I have misunderstood.

Thanks again,

Doris J. Bates, Ph.D.

Regulatory Project Manager

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

-----Original Message-----

From: Siddiqui, Ohidul I
Sent: Friday, April 02, 2004 10:01 AM
To: Khin, Ni Aye; Levin, Robert
Cc: Bates, Doris J
Subject: RE: NDA 21-710 Carbatrol

Hi Ni,

The treatment remained statistically significantly different from placebo (pvalue=.0001) based on only the US 19 sites. So, the Indian sites are not contributing alone the significant result.

Thanks,

Ohid

-----Original Message-----

From: Khin, Ni Aye
Sent: Wednesday, March 31, 2004 4:42 PM
To: Levin, Robert; Siddiqui, Ohidul I
Cc: Bates, Doris J
Subject: NDA 21-710 Carbatrol

Hi Bob and Ohid,

I am thinking about selecting the following domestic sites for inspection:

1) Mark Lerman, MD, Hoffman Estates, IL (site 17, protocol 105.301, 16/16 subj; site 11, protocol

SPD417-304, 10/6 subj)

2) Rajinder Shiwach, MD, Terrell, TX (site 28, protocol 105.301, 25/25 subj; site 20, protocol SPD417-304, 16/14 subj)

Please let me know if you wish to add or change any domestic sites. I plan to initiate inspection request in a couple of weeks.

As discussed during the meeting, I would appreciate if Ohid could let me know with any of the sites from India (site 51 through 56) in protocol SPD417-304 contribute significant efficacy results (i.e., in terms of p-values after removing each of these sites). Thanks.

--Ni

Appears This Way
On Original

Bates, Doris J

From: Lomri, Zohra [ZLomri@us.shire.com]
Sent: Monday, May 10, 2004 4:38 PM
To: 'Bates, Doris J'
Subject: RE: NDA 21-710: NDA Filed: 74-Day Letter Attached To This E-Mail
Good afternoon Doris,

attached is the response to the 74 day letter of April 26 2004. The usual hard copies (review and archival have been sent) and an additional 3 desk copies have been mailed to your attention.

If you have any question, feel free to contact me at your earliest convenience.

Kind Regards

Zohra Lomri
Sr. Manager, Regulatory Affairs
1801 Research Boulevard Suite 600
Tel (240) 453 - 6447
Fax (240) 453 - 6456
Email zlomri@us.shire.com

-----Original Message-----

From: Bates, Doris J [mailto:BATESD@cder.fda.gov]
Sent: Monday, April 26, 2004 5:05 PM
To: Lomri, Zohra
Cc: Bates, Doris J
Subject: RE: NDA 21-710: NDA Filed: 74-Day Letter Attached To This E-Mail

Good afternoon Zohra,

Attached to this email is a .pdf copy of our signed 74-day letter for NDA 21-710. This can be considered an official copy, since the FDA signature process is all electronic.

The letter includes review questions (Biopharmaceutics) and a request for further patent information in connection with the 505(b)(2) status of the NDA.

I will be here tomorrow morning - if you have any questions feel free to contact me. (I will be out of the office all day this Friday).

Very sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

11/28/2004

10 May 2004

Shire

RECEIVED
MAY 11 2004
DDR-120 / CDER

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Center for Drug Evaluation and Research
Woodmont II Building
1451 Rockville Pike
Rockville, Maryland 20852

NDA#: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Response to 74-Day Letter
(Response to Filing Communication Review Issues Identified)
Submission No.: 004

Dear Dr. Katz:

Reference is made to your correspondence of 26 April 2004 regarding our New Drug Application, NDA 21-710 for carbamazepine extended-release capsules (SPD417), which was submitted on 13 February 2004 as Submission No. 000.

Our responses to the filing communication review issues identified are included for your review.

If you have any questions regarding this submission, please contact me at (240) 453 – 6447.

Sincerely,



Zohra Lomri
Senior Manager
Regulatory Affairs

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Shire Laboratories, Inc.	DATE OF SUBMISSION 10 May 2004
TELEPHONE NO. (Include Area Code) (240) 453-6447	FACSIMILE (FAX) Number (Include Area Code) (240) 453-6456
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 1550 East Gude Drive Rockville, MD 20850	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Shire Pharmaceutical Development Inc. 1801 Research Blvd., Suite 600 Rockville, MD 20850

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA 21-710		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Carbamazepine extended-release capsules	PROPRIETARY NAME (trade name) IF ANY Proposed Name: []	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) Carbamazepine extended-release capsules	CODE NAME (if any) SPD417	
DOSAGE FORM: Capsules	STRENGTHS: 100mg, 200mg, 300mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Treatment of acute manic or mixed episodes associated with Bipolar I Disorder		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)		
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Carbatrol (NDA 20-712) Shire Laboratories Inc. Tegretol (NDA 16-608) Holder of Approved Application Novartis		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER		
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION Response to FDA 74-day letter		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC		
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-712 DMF
 IND 59,050 DMF
 IND [redacted] DMF

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50 (e))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Zohra Lomri Senior Manager, Regulatory Affairs	DATE: 10 May 2004
ADDRESS (Street, City, State, and ZIP Code) Shire Pharmaceutical Development Inc. 1801 Research Blvd, Suite 600, Rockville, MD 20850		Telephone Number (240) 453-6447

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Regulatory/Legal

We note that you have cited both Carbatrol (NDA 20-712) and Tegretol (NDA 16-608 as reference listed drugs for this 505(b)(2) application. NDA 16-608 refers to the immediate release dosage form of Tegretol. We are aware that the extended release dosage form of this drug, Tegretol XR (NDA 20-234), was not yet approved or available during the development of Carbatrol, and that the Carbatrol NDA therefore cites the immediate release form of Tegretol as its reference listed drug.

However, Tegretol XR was approved prior to development of the current 505(b)(2) product, SPD417, and, like SPD417, it is administered BID. The current Agency Draft Guidance for 505(b)(2) applications recommends that, if there is a listed drug that is the pharmaceutical equivalent to the drug proposed in a 505(b)(2) application, that drug should be identified as the reference listed drug.

We consider Tegretol XR to be more pharmaceutically equivalent to SPD417 than the Tegretol IR product, and therefore request that you reference and provide certification for the applicable patents for the Tegretol XR product. This certification should specify the exact patent number(s) and the exact name of the listed drug even if all relevant patents have expired.

Please also provide information as per 21 CFR 314.54(a)(1)(iv) regarding the differences in indication and per 21 CFR 314.108(b) with respect to marketing exclusivity, for Tegretol XR.

Shire Response

Shire acknowledges the Agency's interpretation of the statement "if there is a listed drug that is the pharmaceutical equivalent to the drug proposed in a 505(b)(2) application, that drug should be identified as the reference listed drug", however, Shire's understanding of the above statement is that Carbatrol (NDA 20-712) is the closest pharmaceutical equivalent to the proposed SPD417 (NDA 21-710) and is therefore the appropriate reference to use. Shire also understands from the information available through freedom of information, that the Tegretol XR (NDA 20-234) relies extensively on the efficacy and safety information included in Tegretol NDA 16-608, therefore Shire was referencing the source data, Tegretol NDA 16-608. As a result, Shire feels the most relevant NDAs to use during the review of SPD417 are Carbatrol NDA 20-712 and Tegretol NDA 16-608 and that patent certification and reference to Tegretol XR should not be included in this application.

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 [] (formerly referred to as SPD417) 100mg, 200mg, and 300mg using the current approved dissolution procedure for Carbatrol®. For each strength of [] 12 individual dosage units (N=12) were dissolved and sampled at the 1, 2, 4, 6, 8, 10, and 12-hour timepoints. The dissolution profile results from the [] 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 [] and Carbatrol® Dissolution Profiles			
Strength	[] 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

The dissolution profile comparisons resulted in f_2 similarity factors of ≥ 50 , suggesting that the dissolution profiles for the 100mg, 200mg, and 300mg strengths of [] are similar to the dissolution profiles of corresponding strengths of Carbatrol®. Figure 1 through Figure 9 on the following pages show the plots for each individual f_2 similarity comparison.

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9 Page(s) Withheld



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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



4-26-04

NDA 21-710
Rick Lilley, Ph.D.
Senior Vice President, Regulatory Affairs
Shire Pharmaceutical Development, Inc.
1801 Research Boulevard, Suite 600
Rockville, MD 20850

**FILING COMMUNICATION
REVIEW ISSUES IDENTIFIED**

Dear Dr. Lilley:

Please refer to your New Drug Application (NDA), submitted and received on February 13, 2004 under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for SPD 417 (carbamazepine extended-release capsules) 100 mg, 200 mg, and 300 mg.

We also refer to your submissions dated February 19, 2004, March 8, 2004, and March 12, 2004.

We have completed our filing review of your NDA and have determined that your application is sufficiently complete to permit substantive review. Therefore, this application has been filed under section 505(b) of the Act. Our voice mail and secure e-mail correspondence to Zohra Lomri of your firm, dated March 31, 2004, confirmed the filing decision.

In our filing review, we have identified the following review issues:

Regulatory/Legal

We note that you have cited both Carbatrol (NDA 20-712) and Tegretol (NDA 16-608) as reference listed drugs for this 505(b)(2) application. NDA 16-608 refers to the immediate release dosage form of Tegretol. We are aware that the extended release dosage form of this drug, Tegretol XR (NDA 20-234), was not yet approved or available during the development of Carbatrol, and that the Carbatrol NDA therefore cites the immediate release form of Tegretol as its reference listed drug.

However, Tegretol XR was approved prior to development of the current 505(b)(2) product, SPD 417, and, like SPD 417, it is administered BID. The current Agency Draft Guidance for 505(b)(2) applications recommends that, if there is a listed drug that is the pharmaceutical equivalent to the drug proposed in a 505(b)(2) application, that drug should be identified as the reference listed drug.

We consider Tegretol XR to be more pharmaceutically equivalent to SPD 417 than the Tegretol IR product, and therefore request that you reference and provide certification for the applicable patents for the Tegretol XR product. This certification should specify the exact patent number(s) and the exact name of the listed drug even if all relevant patents have expired.

Please also provide information as per 21 CFR 314.54(a)(1)(iv) regarding the difference in indication, and per 21 CFR 314.108(b) with respect to marketing exclusivity, for Tegretol XR.

Biopharmaceutics

Your firm has submitted dissolution data for three lots for each strength of C } -- 100 mg, 200 mg and 300 mg (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 value. This implies testing of one test lot to one lot of the reference and thus obtaining F2 values for each and every lot. This would mean three F2 values for the 100 mg strength, three F2 values for the 200 mg 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.*

We are providing the above comments to inform you of review issues identified to date. Our filing review is only a preliminary evaluation of the application and is not indicative of all deficiencies that may be identified during our substantive review. Issues may be added, expanded upon, or modified as we review the application.

Please respond only to the requests for information listed in this letter. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the actual time of receipt of the submission.

If you have any questions, please feel free to contact Doris J. Bates, Ph.D., Regulatory Project Manager, either by phone at 301-594-2850 or by email at batesd@cdcr.fda.gov.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
4/26/04 04:17:53 PM

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, March 31, 2004 4:34 PM
To: 'Lomri, Zohra'
Cc: Bates, Doris J
Subject: RE: NDA 21-710: NDA Filed

Good afternoon Zohra,

This email is to confirm that the Division met today and agreed that NDA 21-710 is fileable.

The filing date is April 13, but the filing decision was taken today. (Submission date February 13, 2004; receipt date February 13, 2004.) The submission has therefore been filed as of today. You may cite this email as an official communication of the filing decision from the Division.

We will also be sending you a 74-day letter on or before April 27, 2004, which will confirm this information and will include any review questions that have arisen in this interval. I will send you a copy of this letter via secure e-mail as soon as it is officially signed.

The action due date for your NDA is ten months, December 13, 2004. I will be in touch with the 74-day letter and any questions that arise subsequently from the review team.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

3/31/2004

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates
3/31/04 04:33:24 PM
CSO

Shire Pharmaceutical Development Inc

1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

03 March 2004

Doris Bates
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Shire

RECEIVED

MAR - 4 2004

DDR-120 / CDER

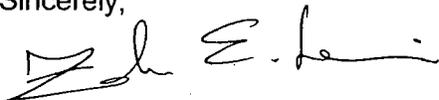
NDA#: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Desk copies
Information requested to facilitate planning of clinical site inspections

Dear Dr. Bates:

Per your email request of February 23, I am enclosing 2 copies of the information needed to facilitate planning for the clinical site(s) inspection. Attached is a list of the requested information with the response.

If you have any questions or require additional information, please contact me at (240) 453 - 6447.

Sincerely,



Zohra Lomri
Senior Manager, Regulatory Affairs

Enclosures

The additional information requested was, for each pivotal study:

1. A list of each clinical site and the name and address of the clinical investigator involved
2. The number of evaluable subjects by site
3. The number of AEs, SAEs, Protocol Violation(s) by site
4. The list of discontinuation of subjects per site and the reason for discontinuation

The pivotal studies are study #105.301 and study #417.304

The following information for the 1st pivotal study #105.301 is provided:

1. **Attachment 1:** *Table 1.1.1. Summary of Investigational Sites Enrollment Duration:* this table lists. This table can also be found in Module 5, Volume 1.1, tab Final Clinical Study Report 105.301, page 91:
 - 1st highlighted column: the site numbers
 - 2nd highlighted column: name of investigator at each site
 - 3rd highlighted column: the site location
 - 4th highlighted column: the number of patients enrolled at each site
2. **Attachment 2:** The complete address of each site per study. This information can also be found in Module 1, Volume 1.1, tab financial disclosure information, page 2.
3. **Attachment 3:** *Table 1.2.2. Study Outcome of All Patients Enrolled by Site, Demographics and Disease Diagnosis.* This table includes the number of discontinuation per site and the reason for discontinuation and can also be found in Module 5, Volume 1.1, tab Final Clinical Study Report 105.301, page 95 .
4. **Attachment 4:** *Table 3.2.11 List of serious adverse events.* This table can also be found in Module 5, Volume 1.1, tab Final Clinical Study Report 105.301, page 252 .
 - The table below summarizes the list of serious adverse for each site

Site	Number of serious AEs
04	1
16	1
24	2
27	1
28	1
29	1
33	1
Total	8

5. **Attachment 5:** Number of AEs reported by site.

The following information for the 2nd pivotal study #417.304 is provided:

6. **Attachment 6:** *Table 1.1.1. Summary of Investigational Sites Enrollment Duration:* this table lists. This table can also be found in Module 5, Volume 1.17, tab Final Clinical Study Report 417.304, page 115:
 - 1st highlighted column: the site numbers
 - 2nd highlighted column: name of investigator at each site
 - 3rd highlighted column: the site location
 - 4th highlighted column: the number of patients enrolled at each site
7. **Attachment 2:** The complete address of each site per study. This information can also be found in Module 1, Volume 1.1, tab financial disclosure information, page 2.
8. **Attachment 7:** *Table 1.2.2. Study Outcome of All Patients Enrolled by Site, Demographics and Disease Diagnosis.* This table includes the number of discontinuation per site and the reason for discontinuation and can also be found in Module 5, Volume 1.17, tab Final Clinical Study Report 417.304, page 119.
9. **Attachment 8:** *Table 3.2.11 List of serious adverse events.*
 - The table below summarizes the list of serious adverse for each site

Site	Number of serious AEs
04	2
05	1
12	3
23	1
24	1
51	1
54	1
Total	10

- **Attachment 9:** Number of AEs reported by site.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Shire Laboratories, Inc.	DATE OF SUBMISSION 03 March 2004
TELEPHONE NO. (Include Area Code) (240) 453-6400	FACSIMILE (FAX) Number (Include Area Code) (240) 453-6456
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 1550 East Gude Drive Rockville, MD 20850	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Shire Pharmaceutical Development Inc. 1801 Research Blvd., Suite 600 Rockville, MD 20850

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **NDA 21-710**

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Carbamazepine extended-release capsules	PROPRIETARY NAME (trade name) IF ANY Proposed Name: []
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Carbamazepine extended-release capsules	CODE NAME (If any) SPD417
DOSAGE FORM: Capsules	STRENGTHS: 100mg, 200mg, 300mg
ROUTE OF ADMINISTRATION: Oral	

(PROPOSED) INDICATION(S) FOR USE:
Treatment of acute manic or mixed episodes associated with Bipolar I Disorder

APPLICATION INFORMATION

APPLICATION TYPE (check one)
 NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Carbatrol (NDA 20-712) Tegretol (NDA 16-608)	Holder of Approved Application Shire Laboratories Inc. Novartis
---	---

TYPE OF SUBMISSION (check one)
 ORIGINAL APPLICATION AMENDMENT TO PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION
Response to request for information to facilitate planning of clinical site inspections

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attachment.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-712	DMF	DMF	DMF	DMF	DMF
IND 59,050	DMF	DMF	DMF	DMF	DMF
IND []	DMF	DMF	DMF	DMF	DMF

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify): Information to facilitate planning of clinical site inspections

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Zohra Lomri Senior Manager, Regulatory Affairs	DATE: 03 March 2004
ADDRESS (Street, City, State, and ZIP Code) Shire Pharmaceutical Development Inc. 1801 Research Blvd, Suite 600, Rockville, MD 20850		Telephone Number (240) 453-6447

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Attachment to Form FDA 3454

Protocol No. SLI105.301		
Investigators	Affiliation	Address
Principal Investigator: J. Gary Booker, M.D. Sub-investigators: []	GGS Research Clinic, LLC	827 Margaret Place, Suite 207 Shreveport, AL 71101
Principal Investigator: Christopher S. Kelsey, M.D. Sub-investigators: []	San Diego Center for Research	3969 Fourth Avenue, Suite 203 San Diego, CA 92103
Principal Investigator: Timothy Reid, M.D. Sub-investigators: []	Clinical Studies, Melbourne	1360 Sarno Road, Suite B Melbourne, FL 32935
Principal Investigator: Stanley Cheren, M.D. Sub-investigators: []	The Clinical Studies Unit MetroWest Medical Center	67 Union Street Natick, MA 01760

Protocol No. SLI105.301 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Ronald Brenner, MD Sub-investigators: []	Neurobehavioral Research, Inc. St. John's Episcopal Hospital South Shore	327 Beach 19 th Street Far Rockaway, NY 11691
Principal Investigator: Teresa Pigott, MD Sub-investigators: []	Comprehensive NeuroScience, Inc.	4701 Willard Avenue, Suite 105 Chevy Chase, MD 20815

Protocol No. SLI105.301 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: David A. Sack, MD Sub-investigators: [Institute for Psychopharmacology Research of Orange County	11050 E. Artesia Blvd, Suite G Cerritos, CA 90703
Principal Investigator: Louis F. Fabre, MD, Ph.D. Sub-investigators: [Fabre Research Clinics, Inc.	5503 Crawford Houston, TX 77004
Principal Investigator: Saaid Khojasteh, MD Sub-investigators: [Dr. Saaid Khojasteh and Associates	330 First Capitol, Suite 410 St. Charles, MO 63301
Principal Investigator: Robert A. Riesenber, MD Sub-investigators: [Atlanta Center for Medical Research	625 Dekalb Industrial Way Decatur, GA 30033

Protocol No. SLI105.301 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Joseph G. Fanelli, MD Sub-investigators: []	Midwest Center for Neurobehavioral Medicine	18 W. 100 Twenty Second Street, Suite 126 Oakbrook Terrace, IL 60181
Principal Investigator: Mark B. Hamner, MD Sub-investigators: []	Ralph H. Johnson VA Medical Center Psychiatry Service (116)	109 Bee Street Charleston, SC 29401
Principal Investigator: M. Afzar Malik, MD, MBA Sub-investigators: []	Psych Care Consultants LLC	621 S. New Ballas Rd Suite 398 St. Louis, MO 63141 []
Principal Investigator: Rakesh Ranjan, MD Sub-investigators: []	Psychobiology Clinic of Greater Cleveland, Inc.	2940 Noble Road, Suite 200 Cleveland Heights, OH 44121 []
Principal Investigator: Joseph P. McEnvoy, MD Sub-investigators: []	John Umstead Hospital	1003 12 th Street Butner, NC 27509

Protocol No. SLI105.301 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Jasbir S. Kang, MD Sub-investigators: ()	Allegheny Behavioral Health Associates	1260 Broadhead Road Monaca, PA 15061 150 Pleasant Drive Aliquippa, PA 15001
Principal Investigator: Alan C. Swann, MD Sub-investigators: 	University of Texas Health Science Center Department of Psychiatry and Behavioral Sciences	1300 Moursund Ave Room 270 Houston, TX 77030
Principal Investigator: Michael G. Plopper, MD Sub-investigators: L	Sharp Mesa Vista Hospital	7850 Vista Hill Avenue San Diego, CA 92123

Protocol No. SL105.301 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Carlos Figueroa, MD Sub-investigators: []	BHC Alhambra Hospital	4619 N. Rosemead Blvd Rosemead, CA 91770
Principal Investigator: Alia Karim, M.D. Sub-investigators: []	L.A. Metropolitan Medical Center	13300 South Hawthorne Blvd. Hawthorne, CA 90250
Principal Investigator: Adam F. Lowy, MD Sub-investigators: []	Comprehensive NeuroScience, Inc.	4228 Wisconsin Ave. NW Washington, DC 20016

Protocol No. SLI105.302 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Mohammed A. Bari, MD Sub-investigators: []	Synergy Clinical Research Center	450 Fourth Avenue Suite 409 Chula Vista, CA 91910
Principal Investigator: William John Privitera, MD Sub-investigators: []	Future Search Trials	4200 Marathon Blvd. Suite 200 Austin, TX 78756
Principal Investigator: William C. Fuller, M.D. Sub-investigators: []	University Physicians Department of Psychiatry	1310 W. 22 nd Street Sioux Falls, SD 57105

Protocol No. SLI105.303 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Alan F. Jacobson, Ph.D. Sub-investigators: []	Allied Clinical Trials, Inc	1385 NW 15 th Street Miami, FL 33125
Principal Investigator: Christopher S. Kelsey, M.D. Sub-investigators: []	San Diego Center for Research	3969 Fourth Avenue, Suite 203 San Diego, CA 92103
Principal Investigator: Mark N. Lerman, M.D. Sub-investigators: []	Linden Oaks Hospital	852 West Street Naperville, IL 60540
Principal Investigator: William J. Privitera, M.D. Sub-investigators: []	[]	706 West MLK Jr Blvd., #7 Austin, TX 78701 []

Protocol No. SLI105.303 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Richard H. Weisler, MD Sub-investigators: []	Private Practice	900 Ridgefield Drive Suite 320 Raleigh, NC 27609
Principal Investigator: Ronald Brenner, MD Sub-investigators: []	Neurobehavioral Research, Inc. St. John's Episcopal Hospital South Shore	327 Beach 19 th Street Far Rockaway, NY 11691
Principal Investigator: Teresa Pigott, MD Sub-investigators: []	Comprehensive NeuroScience, Inc.	4701 Willard Avenue, Suite 105 Chevy Chase, MD 20815
Principal Investigator: Alan F. Jacobson, Ph.D. Sub-investigators: []	Allied Clinical Trials, Inc.	1385 NW 15 th Street Miami, FL 33125

Protocol No. SLI105.303 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: James M. Russell, MD Sub-investigators: []	University of Texas Medical Branch Department of Psychiatry and Behavioral Sciences	301 University Blvd (RSH 3.266) Galveston, TX 77555
Principal Investigator: James M. Russell, MD Sub-investigators: []	University of Texas Medical Branch Department of Psychiatry and Behavioral Sciences	301 University Blvd (RSH 3.266) Galveston, TX 77555
Principal Investigator: Terence A. Ketter, MD Sub-investigators: []	Psychiatry and Behavioral Sciences Stanford University	401 Quarry Road Suite 2124 Stanford, CA 94305

Protocol No. SLI105.303 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Adam F. Lowy, MD Sub-investigators: []	Comprehensive NeuroScience, Inc.	4228 Wisconsin Ave. NW Washington, DC 20016
Principal Investigator: John H. Gilliam, MD Sub-investigators: []	International Clinical Research Associates, Inc.	7650 E. Parham Road Medical Office Building #2 Suite 240 Richmond, VA 23294

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Protocol No. SPD417.304 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Arifulla Khan, MD Sub-investigators: [Northwest Clinical Research Center	1900 116 th Ave. NE Bellevue, WA 98004
Principal Investigator: Mark Lerman, MD Sub-investigators: [Alexian Brothers Behavioral Health Hospital	1650 Moon Lake Blvd Hoffman Estates, IL 60194

Protocol No. SPD417.304 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Louis Beckett, MD Sub-investigators: []	IPS Research Company	1211 N. Shartel Suite 407 Oklahoma City, OK 73103
Principal Investigator: David W. Brown, MD Sub-investigators: []	Community Clinical Research, Inc.	4411 Medical Parkway Austin, TX 78756
Principal Investigator: Thomas Gazda, MD Sub-investigators: []	St. Luke's Behavioral Health Center	1800 E. Van Burren Ave. Phoenix, AZ 85006

Protocol No. SPD417.304 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: David M. Marks, MD Sub-investigators: []	Optimum Health Services	7200 Parkway Drive Suite 116 La Mesa, CA 91942
Principal Investigator: Denis Mee-Lee, MD Sub-investigators: []	Hawaii Clinical Research Center	1750 Kalakaua Avenue Suite 2602 Honolulu, HI 96826
Principal Investigator: Michael G. Plopper, MD Sub-investigators: []	Sharp Mesa Vista Hospital	7850 Vista Hill Avenue San Diego, CA 92123
Principal Investigator: Raj S. Shiwach, MD Sub-investigators: []	Terrell State Hospital Research Center	1200 E. Brin Street Terrell, TX 75160

Protocol No. SPD417.304 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Craig J. Wronski, DO Sub-investigators: []	California Neuropsychopharmacology Clinical Research Institute-LA, LLC	8337 Telegraph Road Suite 319 Pico Rivera, CA 90660
Principal Investigator: Dr Nadukuru Nooka Raju Sub-investigators: []	Government Hospital for Mental Care	China Waltair, Visakhapatnam, Andhra Pradesh, 530 017 India
Principal Investigator: Jitendra Kumar Trivedi, MD Sub-investigators: []	Department of Psychiatry Chhatrapati Shahuji Maharaj Medical University and Gandhi Memorial and Associated Hospitals	Lucknow, 226 003 India
Principal Investigator: Dr Jitendra Nagpal Sub-investigators: []	Vidyasagar Institute of Mental Health and Neurosciences	No. 1 Institutional Road Nehru Nagar New Delhi, 110 065 India
Principal Investigator: Dr PSVN Sharma Sub-investigators: []	Department of Psychiatry Kasturba Hospital	Manipal, 576 119 Karnataka India

Protocol No. SPD417.304 (cont'd)		
Investigators	Affiliation	Address
Principal Investigator: Mark H. Townsend, MD	LSU Health Sciences Center Department of Psychiatry	1542 Tulane Avenue New Orleans, LA 70112
Sub-investigators: []		

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Table 1.2.2 Study Outcome of All Patients Enrolled by Site, Demographics, and Disease Diagnose

Total	Complete	Total	Lost Follow-up	AE	Early Termination					Death	Other
					Subject Choice	Failed P. Lead in	Lack of Efficacy	Protocol Violation			
267	96 (36%)	171 (64%)	6 (2%)	20 (7%)	61 (23%)	31 (12%)	36 (13%)	4 (1%)	0 (0%)	13 (5%)	
Site											
01	9 (41%)	13 (59%)	1 (5%)	0 (0%)	6 (27%)	6 (27%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
04	1 (14%)	6 (86%)	0 (0%)	0 (0%)	4 (57%)	1 (14%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	
05	5 (42%)	7 (58%)	0 (0%)	2 (17%)	3 (25%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
06	6 (50%)	6 (50%)	2 (17%)	1 (8%)	0 (0%)	1 (8%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)	
08	3 (33%)	2 (67%)	0 (0%)	0 (0%)	2 (67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
11	1 (9%)	10 (91%)	1 (9%)	1 (9%)	3 (27%)	1 (9%)	2 (18%)	1 (9%)	0 (0%)	1 (9%)	
13	2 (15%)	11 (85%)	0 (0%)	1 (8%)	3 (23%)	5 (38%)	2 (15%)	0 (0%)	0 (0%)	0 (0%)	
15	3 (75%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	
16	0 (0%)	10 (100%)	0 (0%)	2 (20%)	3 (30%)	2 (20%)	1 (10%)	0 (0%)	0 (0%)	2 (20%)	
17	9 (56%)	7 (44%)	0 (0%)	3 (19%)	1 (6%)	0 (0%)	2 (13%)	0 (0%)	0 (0%)	1 (6%)	
19	5 (0%)	5 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (100%)	0 (0%)	0 (0%)	0 (0%)	
20	6 (38%)	10 (63%)	0 (0%)	1 (6%)	6 (38%)	0 (0%)	1 (6%)	1 (6%)	0 (0%)	1 (6%)	
21	0 (0%)	2 (100%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	
24	4 (22%)	14 (78%)	0 (0%)	3 (17%)	7 (39%)	0 (0%)	3 (17%)	1 (6%)	0 (0%)	0 (0%)	
25	5 (71%)	2 (29%)	0 (0%)	0 (0%)	1 (14%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
26	3 (33%)	2 (67%)	0 (0%)	0 (0%)	1 (33%)	1 (33%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
27	10 (45%)	12 (55%)	0 (0%)	2 (9%)	1 (5%)	8 (36%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	
28	9 (36%)	16 (64%)	0 (0%)	1 (4%)	5 (20%)	0 (0%)	10 (40%)	0 (0%)	0 (0%)	0 (0%)	
29	2 (20%)	8 (80%)	0 (0%)	0 (0%)	3 (30%)	1 (10%)	4 (40%)	0 (0%)	0 (0%)	0 (0%)	
30	13 (68%)	6 (32%)	1 (5%)	0 (0%)	2 (11%)	1 (5%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	
31	2 (18%)	9 (82%)	1 (9%)	1 (9%)	4 (36%)	0 (0%)	0 (0%)	1 (9%)	0 (0%)	2 (18%)	
33	3 (43%)	4 (57%)	0 (0%)	0 (0%)	2 (29%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	
34	4 (80%)	1 (20%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
37	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	
38	0 (0%)	2 (100%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	
39	0 (0%)	2 (100%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
40	0 (0%)	2 (100%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	

Gender
 Female 135 44 (33%) 91 (67%) 1 (1%) 11 (8%) 37 (27%) 16 (12%) 17 (13%) 1 (1%) 0 (0%) 8 (6%)
 Male 132 52 (39%) 80 (61%) 5 (4%) 9 (7%) 24 (18%) 15 (11%) 19 (14%) 3 (2%) 0 (0%) 5 (4%)
 TPR=Terminated Prior to Randomization.

PROGRAM: T_ACC02.SAS FILENAME: T_ACC02A2.DOC

(Continued)

Table 3.2.11 List of Serious Adverse Events

Study Group	Subject ID	Age (yrs)	Sex	Reported Term [Preferred Term (COSTART)]	Week Occurred	Duration Drug (days) Relation	Severity	Effect on Dose	Treatment	Serious
Carbatrol®	016-007	44	Male	EXACERBATION OF BIPOLAR DISORDER MANIC [MANIC REACTION]	4	5 Unrelated	Moderate	Rx Stopped	Hospitalized	Hospitalization
	024-004	38	Female	WORSENING OF BIPOLAR ILLNESS [MANIC REACTION]	1	3 Unrelated	Severe	Rx Stopped	Hospitalized	Hospitalization
				WORSENING OF BIPOLAR ILLNESS [MANIC REACTION]	3	10 Unrelated	Severe	Rx Stopped	Hospitalized	Hospitalization
	027-016	43	Female	WORSENING OF BIPOLAR DISORDER SYMPTOMS [MANIC DEPRESS REACT]	2	6 Unrelated	Moderate	Rx Stopped	Rx Therapy	Hospitalization
	033-007	36	Female	EXACERBATION OF BIPOLAR I [MANIC DEPRESS REACT]	3	4 Unrelated	Severe	None	Hospitalized	Hospitalization
Placebo	004-004	55	Female	REHOSPITALIZATION FOR SUICIDALITY [DEPRESSION]	2	6 Unrelated	Moderate	None	Hospitalized	Hospitalization
	024-002	36	Male	WORSENING OF BIPOLAR ILLNESS (DEPRESSIVE SYMPTOMS) [DEPRESSION]	2	2 Unrelated	Severe	Rx Stopped	Hospitalized	Hospitalization
	028-025	27	Female	EXACERBATION OF BIPOLAR MANIA [MANIC REACTION]	5	11 Unrelated	Moderate	None	Hospitalized	Hospitalization
	029-008	26	Female	EXACERBATION OF BIPOLAR SYMPTOMS [MANIC REACTION]	3	14 Unrelated	Moderate	Rx Stopped	Hospitalized	Hospitalization

PROGRAM: T_AES05.SAS FILENAME: T_AES05A1.DOC

Final

Date: November 2, 2001

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12 March 2004



Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Center for Drug Evaluation and Research
Woodmont II Building
1451 Rockville Pike
Rockville, Maryland 20852

NDA#: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Amendment to a Pending Application:
Photostability Data
Submission No.: 003

Dear Dr. Katz:

Reference is made to a New Drug Application (NDA) for SPD417, NDA 21-710, which was submitted on 13 February 2004 as Submission No. 000.

Reference is also made to a telephone conversation with the Chemistry Reviewer, Dr. Chhagan Tele, on 5 March 2004. Enclosed, please find photostability data of the finished product as requested by Dr. Tele.

Shire certifies that a field copy of the CMC section has been sent to the Baltimore field office.

If you have any questions regarding this submission, please contact me at (240) 453 - 6447.

Sincerely,

A handwritten signature in black ink, appearing to read "Zohra Lomri".

Zohra Lomri
Senior Manager
Regulatory Affairs

Enclosures

Shire Pharmaceutical Development Inc
1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

8 March 2004

The Shire logo consists of a stylized, bold, black letter 'S' with a white swoosh that curves around its top and left side, followed by the word 'Shire' in a bold, sans-serif font.

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Center for Drug Evaluation and Research
Woodmont II Building
1451 Rockville Pike
Rockville, Maryland 20852

NDA#: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Amendment to a Pending Application
Submission No.: 001

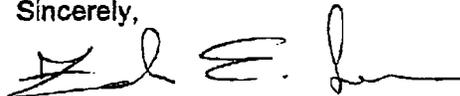
Dear Dr. Katz:

Reference is made to a New Drug Application (NDA) for SPD417, NDA 21-710, which was submitted on 13 February 2004 as Submission No. 000. Enclosed, please find colored copies of Patient Sample labels for 100mg (14 count), 200mg (30 count), and 300mg (30 count).

Shire expects a change in design at a later date as we develop the branding for the product. However, the text will not change.

If you have any questions regarding this submission, please contact me at (240) 453 - 6447.

Sincerely,

A handwritten signature in black ink, appearing to read 'Zohra Lomri', written in a cursive style.

Zohra Lomri
Senior Manager
Regulatory Affairs

Enclosures

Shire Pharmaceutical Development Inc
 1801 Research Boulevard Suite 600 Rockville MD 20850 USA
 Tel 240 453 6400 Fax 240 453 6404

12 March 2004



Russell Katz, M.D.
 Division Director
 Division of Neuropharmacological Drug Products (HFD-120)
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Woodmont II Building
 1451 Rockville Pike
 Rockville, Maryland 20852

NDA#: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
 100mg, 200mg, 300mg
Type of Submission: Amendment
 Withdrawal of as an
 site (Registration #
Submission No.: 002

Dear Dr. Katz:

Reference is made to a New Drug Application (NDA) for SPD417, NDA 21-710, which was submitted on 13 February 2004 as Submission No. 000. Shire does not intend to use as a site for SPD417 Extended-release Capsules 200 mg and 300 mg (Registration No.:). Therefore, Shire is withdrawing as a proposed site for the of SPD417 Extended-release Capsules 200 mg and 300 mg from this submission.

Shire certifies that a field copy of the CMC section has been sent to the Baltimore field office.

If you have any questions regarding this submission, please contact me at (240) 453 - 6447.

Sincerely,



Zohra Lomri
 Senior Manager
 Regulatory Affairs

Enclosures

Shire Pharmaceutical Development Inc
1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

19 February 2004



Central Document Room (HFD-94)
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

NDA# 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Amendment to Original New Drug Application
Resubmission of Electronic Files

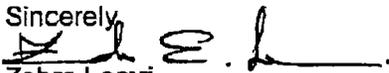
Dear Electronic Document Room Staff:

In accordance with 21 CFR 314.50, Shire Pharmaceutical Development Inc., a subsidiary of Shire Laboratories Inc., has submitted an original 505 (b)(2) New Drug Application (NDA) for carbamazepine extended-release capsules, 100mg, 200mg, and 300mg, the subject of IND #59,050. Reference is made to Shire's NDA for Carbatrol® (NDA #20-712) and Novartis' NDA for Tegretol® (NDA #16-608).

The original application was provided as a paper application in CTD format, with the exception of the Case Report Forms (CRFs) and Case Report Tabulations (CRTs) on February 13, 2004. Shire is resubmitting in electronic eNDA format the electronic data (Item 11: CRT and Clnstat (courtesy copy), a courtesy copy of the Proposed Prescribing Information, Trade Name Proposal and Rationale, Clinical Summaries of Efficacy and safety and Clinical Study Reports as requested by the Agency.

If you have any questions regarding this submission, please contact me at (240) 453 - 6447.

Sincerely,


Zohra Lomri
Senior Manager
Regulatory Affairs

Enclosures

23 Page(s) Withheld



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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

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this page is the manifestation of the electronic signature.**

/s/

Doris Bates

2/23/04 03:04:59 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): HFD-420 (ODS/DMETS)			FROM: HFD-120 (Dr. Bates)	
DATE Feb. 23, 2004	IND NO.59,050	NDA NO. 21-710	TYPE OF DOCUMENT new NDA submission - Proprietary name consult	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. Labeling review consult requested by November 19, 2004
NAME OF FIRM: Shire Pharmaceutical Development, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: This is a submission from Shire, manufacturer of Carbatrol (carbamazepine, anti-epileptic) for the use of carbamazepine in the treatment of acute manic and mixed episodes associated with bipolar disorder, under the proposed trademark [] A trademark consult has been submitted to DDRE. The submission contains a copy of the current package insert for Carbatrol, the proposed, insert, a side by side comparison of both, and copies of container labeling. Please see the last section in hard copy volume for color copies of container labeling... Links to EDR may not be live in DFS rendering of this form. Please note this is a hybrid (part electronic, part paper) submission and the EDR does not contain all trademark related materials. Please also note that the EDR submission was extensively amended on Feb. 19. <u>.\CDSESUB1\N21710\N 000\2004-02-13</u> <u>.\CDSESUB1\N21710\N 000\2004-02-19</u>				
SIGNATURE OF REQUESTER see DFS signature			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

Doris Bates
2/23/04 03:56:51 PM

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-420 (ODS/DMETS)

FROM: HFD-120 (Dr. Bates)

DATE October 13, 2004

IND NO.59,050

NDA NO. 21-710

TYPE OF DOCUMENT
new NDA submission -
Proprietary name consult
(2nd time)

DATE OF DOCUMENT
Feb. 13, 2004

NAME OF DRUG
carbamazepine

PRIORITY CONSIDERATION

CLASSIFICATION OF
DRUG antimanic

DESIRED COMPLETION DATE:
Action due date December 13, 2004.
Trademark consult feedback requested
by November 19, 2004

NAME OF FIRM: Shire Pharmaceutical Development, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

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

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We are re-submitting the consult for the proposed trademark  submitted by Shire, manufacturer of Carbatrol (carbamazepine, anti-epileptic) for the use of carbamazepine in the treatment of acute manic and mixed episodes associated with bipolar disorder. This consult was previously requested on February 23, 2004. A copy of the initial consult review is attached electronically to this request for your convenience.

No new information has been received from the firm regarding the trademark or labels at this time. The firm has been informed of the Agency's objection to the proposed trademark as per the initial consult review. A re-review is now being requested because the initial feedback was received more than 90 days prior to the action date of December 13, 2004 and therefore a second review is needed prior to the due date.

Link to original EDR submission may not be live in DFS rendering of this form. Please note this is a hybrid (part electronic, part paper) submission and the EDR does not contain all trademark related materials. \\CDSESUB1\N21710\N 000\2004-02-13

SIGNATURE OF REQUESTER see DFS signature

METHOD OF DELIVERY (Check one)

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/s/

Doris Bates
10/13/04 04:56:13 PM

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-710 (Dr. Jin)

FROM: HFD-120 (Dr. Bates)

DATE Feb. 20, 2004

IND NO.59,050

NDA NO. 21-710

TYPE OF DOCUMENT
new NDA submission

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

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

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|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input checked="" type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Link to EDR: May not be live in DFS rendering. Submission does appear to contain electronic datasets.
Please let the CSO know who the stats reviewer will be so that they can be added to the meeting notice.

\\CDSESUB1\N21710\N 000\2004-02-13

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METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Doris Bates
2/20/04 04:34:41 PM

Shire Pharmaceutical Development Inc

1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

13 February 2004



Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Attn: Dr. Russell Katz

NDA#: 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Original New Drug Application
Submission No.: 000

Dear Dr. Katz:

In accordance with 21 CFR 314.50, Shire Pharmaceutical Development Inc., a subsidiary of Shire Laboratories Inc., is submitting this original 505 (b)(2) New Drug Application (NDA) for carbamazepine extended-release capsules, 100mg, 200mg, and 300mg, the subject of IND #59,050. Reference is made to Shire's NDA for Carbatrol® (NDA #20-712) and Novartis' NDA for Tegretol® (NDA #16-608). This application is provided as a paper application in CTD format with the exception of the Case Report Forms (CRFs) and Case Report Tabulations (CRTs), which will be provided in electronic eNDA format. Shire believes this NDA complies with regulatory requirements and is reflective of comments and suggestions received by the sponsor during the development process.

Technical Section Comments

Shire Pharmaceutical Development Inc. has followed recommendations made by the Agency at pre-NDA meetings held on 01 November 2001 and 13 November 2003.

The CMC section and its summary are in traditional NDA format at the request of the reviewers. Both are cross-referenced to Shire's NDA for Carbatrol (NDA #20-712) with the exception of information including comparative dissolution profile of SPD417 and Carbatrol for the three proposed strengths. Bioequivalence and stability requirements were waived since the color change for SPD417 capsules is ± 1 within each strength. Additionally, the most current specifications for carbamazepine, the drug substance, is included as requested during 13 November 2003 meeting with the Agency.

The Nonclinical Pharmacology and Toxicology package is provided in paper CTD format and consist of evaluation of open literature studies in addition to a cross-reference to Carbatrol NDA (NDA #20-712) and Tegretol NDA (NDA #16-608).

Human pharmacokinetics and bioavailability package is provided in paper CTD format and consists of evaluation of data from open literature sources.

The Clinical package is provided in paper CTD format with the exception of the CRFs and CRTs (SAS datasets and patient profiles), provided in eNDA format electronically. Additional book marked electronic copies of the Summary of Clinical Efficacy, the Summary of Clinical Safety and Clinical Study Reports are also included at the reviewers' request. No 120-day update is needed since there are no ongoing trials.

Readers Guide to NDA 21-710

A guide that provides the reviewer with an overview of the structure format, indexing pagination conventions and locations of the electronic documents is provided as an attachment to this letter.

Administrative Information and Labeling

Shire certifies that a field copy of the CMC section has been sent to the Baltimore field office. Certifications concerning debarment, patent information and certification, marketing exclusivity statement, and financial disclosure are included in Module 1, Volume 1 of this application. User fees for this product have been paid and their receipt has been confirmed.

Also included in Module 1, Volume 1 of this application is the pediatric use information, biowaiver request, claim for categorical exclusion, labeling and proposed trade name rationale.

Confidentiality

Shire's expectation is that the usual measures for protecting the confidential nature of this document will be followed by FDA.

Product and Company's name Appearing in this submission

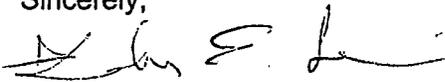
SPD417, carbamazepine extended-release capsules and Carbatrol can be used interchangeably. [REDACTED], the proposed trade name is also used in this application. Shire understands that the proposed trade name of [REDACTED] is subject to comment from the APDRA committee and the Neuropharmacological Drug Products Divisions.

Page 3
NDA 21-710 (SPD417)
Original NDA Application

Thank you for the time already spent by your Division in the course of this product's development. We look forward to your review.

If you have any questions regarding this submission, please contact Zohra Lomri at (240) 453 – 6447.

Sincerely,



for Rick Lilley, Ph.D.
Senior Vice President
Regulatory Affairs

Enclosures

This guide provides the reviewer with an overview of the structure, format, indexing and pagination conventions of this application

Organization of this NDA 21-710

This NDA consists of 46 volumes and follows the contents of the Application as described in **Guidance for Industry *Submitting Marketing Applications According to the ICH-CTD Format – General Considerations*** (draft guidance, August 2001).

Accordingly, this application consists of:

Administrative Information (Module 1): 1 volume

Note: electronic copies of the labels/labeling are provided in addition to an electronic copy of the proposed trade name rationale.

**Summaries of Quality, Nonclinical and Clinical Information (Module 2):
2 volumes**

Quality (CMC) Information (Module 3): 1 volume

Note: the CMC information is provided following the table of content of the traditional NDA format at the reviewer's request

Preclinical Information (Module 4): 1 volume

Clinical Information (Module 5): 41 volumes

Note: the CRFs and CRTs (SAS datasets and patient profiles), provided in eNDA format electronically. Additional bookmarked electronic copies of the Summary of Clinical Efficacy, the Summary of Clinical Safety and Clinical Study Reports

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SHIRE PHARMACEUTICAL DEVELOPMENT, INC.

COMMON TECHNICAL DOCUMENT

NDA 21-710

SPD417

Module 1

Administrative and Prescribing Information

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Module 1: Administrative and Prescribing Information	1	1
Form FDA-356h	1	1
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Marketing Exclusivity	1	1
Debarment Certification	1	1
Field Copy Certification	1	1
User Fee Cover Sheet	1	1
Financial Disclosure Information	1	1
Letters of Authorization	1	1
Biowaiver Request	1	1
Claim for Categorical Exclusion	1	1
Establishment Description	1	1
Pediatric Use Information	1	1

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Annotated Labeling for SPD417	1	1
Carbatrol Package Insert Rev. 8/2003	1	1
Prescribing Information Comparison	1	1
Bottle Labels	1	1
Trade Name Proposal and Rationale	1	1

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Shire Pharmaceutical Development Inc

1801 Research Boulevard Suite 600 Rockville MD 20850 USA
Tel 240 453 6400 Fax 240 453 6404

13 February 2004



Central Document Room (HFD-94)
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

NDA# 21-710
Product Name: SPD417 (carbamazepine extended-release capsules)
100mg, 200mg, 300mg
Type of Submission: Original New Drug Application

Dear Electronic Document Room Staff:

In accordance with 21 CFR 314.50, Shire Pharmaceutical Development Inc., a subsidiary of Shire Laboratories Inc., has submitted an original 505 (b)(2) New Drug Application (NDA) for carbamazepine extended-release capsules, 100mg, 200mg, and 300mg, the subject of IND #59,050. Reference is made to Shire's NDA for Carbatrol® (NDA #20-712) and Novartis' NDA for Tegretol® (NDA #16-608).

The application was provided as a paper application in CTD format, with the exception of the Case Report Forms (CRFs) and Case Report Tabulations (CRTs), which is being provided in electronic eNDA format as attached. Shire is also providing a courtesy copy of the Proposed Prescribing Information, Trade Name Proposal and Rationale, Clinical Summaries of Efficacy and safety and Clinical Study Reports as requested by the Agency.

If you have any questions regarding this submission, please contact me at (240) 453 - 6447.

Sincerely,

A handwritten signature in black ink, appearing to read "Zohra Lomri", is written over a horizontal line.

Zohra Lomri
Senior Manager
Regulatory Affairs

Enclosures