CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 20712

Trade Name CARBATROL

Generic Name Carbamazepine extended release capsules

Sponsor SHIRE LABORATORIES

Approval Date SEPTEMBER 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Medical Review(s)	X			
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Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20712

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-712

Shire Laboratories
Attention: Saundra Geroux
1550 East Gude Drive
Rockville, MD 20850

SEP 30 1997

Dear Ms. Geroux:

Please refer to your new drug application dated April 3, 1996, received April 3, 1996, and to your amendment dated May 19, 1997, received May 20, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carbatrol® (carbamazepine extended-release capsules) 200mg and 300mg.

Reference is also made to the Agency's Approvable Letter dated March 20, 1997.

We acknowledge receipt of your additional correspondence and amendments dated:

March 27, 1997
June 18, 1997
June 23, 1997
August 13, 1997
September 2, 1997

The User Fee goal date for your original submission was April 3, 1997. The User Fee goal date for your amendment is November 20, 1997.

This new drug application provides for an extended-release capsule formulation of carbamazepine for use as an anticonvulsant drug and in the treatment of pain associated with true trigeminal neuralgia.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

Labeling

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-712. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Chemistry, Manufacturing, and Controls

The tentative expiration dating period for Carbatrol capsules is 24 months, calculated from date of initial

Phase 4 Commitment

We remind you of your Phase 4 commitment specified in your submission dated August 13, 1997. This commitment, along with the agreed upon completion date, is listed below.

This data should be submitted in a final report to this NDA as correspondence.

In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of your commitment. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Other

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product (container and carton only) when it is

Please submit one market package of the drug product (container and carton only) when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20712

APPROVABLE LETTER

Ms. Ware

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-712

Pharmavene Inc.
Attention: Saundra Geroux
1550 East Gude Drive
Rockville, MD 20850

MAR 20 1997

Dear Ms. Geroux:

Please refer to your new drug application dated April 3, 1996, received April 3, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carbatrol® (carbamazepine extended-release capsules), 200mg and 300mg. (Please refer to Item 9 under Chemistry, Manufacturing, and Controls for comments regarding nomenclature.)

We acknowledge receipt of your submissions dated:

April 3, 1996	September 30, 1996	December 26, 1996
April 18, 1996	October 2, 1996	January 22, 1997
May 23, 1996	October 11, 1996	February 6, 1997 (2)
August 2, 1996	November 20, 1996	February 13, 1997
September 19, 1996	December 20, 1996	

The User Fee goal date for this application is April 3, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following requests or comments.

Chemistry, Manufacturing and Controls

We have reviewed the February 13, 1997 amendment submitted in response to our February 4, 1997 information request letter. We have the following comments:

1. With respect to Items 5a and 5b in your response, we do not agree that performing

e. Restatement of Items 5a and 5b from 04-Feb-97 Agency letter to Pharmavene:

2. With respect to Item 5c in your response, we have reviewed the

3. With respect to Item 6 in your response, we do not agree that

4. With respect to Item 8 in your response, we have the following comments:

5. With respect to Item 10 in your response, we believe that

6. With respect to Item 11 in your response, the data cited in the 13-Feb-97 amendment was reviewed when the

7. With respect to Item 12 in your response, materials may be accepted based on a supplier's certificate of analysis (CoA). If materials are accepted based on a supplier's certificate of analysis, identity testing, e.g., used, and inspection for cleanliness is *required* for every lot received.

8. With respect to Item 7 and Item 13 in your response, we have reviewed the

9. With respect to Item 14 in your response, we concur with the CDER nomenclature committee recommendation concerning use of the established name "Carbamazepine Extended-Release Capsules". Use of the term is not acceptable. The USP recognizes two designations for modified release dosage forms, extended-release and delayed release (for enteric coated products).

10. With respect to Item 15 in your response, the format suggested, i.e.,

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Carbatrol® upon its approval. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA and in your December 26, 1996 amendment, other sections have been extensively revised and/or expanded to include new subsections. It will be necessary for you to submit revised draft labeling identical in content to the attached draft labeling in response to this letter.

Please note that the pregnancy category for carbamazepine has been changed from pregnancy category C to pregnancy category D. We feel that this drug meets the "Pregnancy Category D" definition as described under 21 CFR 207.57(f)(6)(i)(*d*), and have edited the labeling accordingly.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Safety Update

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

The following comments are provided to assist you in the development of a meaningful

Biopharmaceutics

Promotional Material

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5793.

Sincerely yours,

3/20/97

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

cc:

Original NDA 20-712
HFD-120/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-120/J.Ware
HFD-120/Leber/Katz/McCormick/Blum/Heimann/Fitzgerald/Fisher
HFD-860/Hossain/Mahmood
HFD-101/Office Director
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/OTC (with labeling - for OTC Drug Products Only)

Drafted by: JHW/February 7, 1997/20712ae.ll
Final: 3/6/97; 3/20/97

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20712

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA No:	**20-712**
Sponsor:	**Pharmavene, Inc.**
Brand Name (generic)	**Carbatrol (carbamazepine)**
Indication:	**Epilepsy** ***Partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic-clonic seizures, and mixed seizure patterns which include the above, or other partial or generalized seizures.***
NDA Classification:	**IS**
Original Receipt Date	**April 3, 1996**
Clinical Reviewer	**Cynthia G. McCormick, MD** Cynthia G. McCormick 2/3/97

0.0 Overview

This is an application for marketing a formulation for controlled release carbamazepine, Carbatrol, by a new manufacturer[1], Pharmavene, Inc utilizing a process different from that which was approved for the manufacture of the recently approved product. Carbamazepine is an antiepileptic drug product and an agent approved as an analgesic in the treatment of trigeminal neuralgia. It was first approved in 1974 for oral use, and supplements have included approval of the chewable tablets and most recently extended release formulation. Pharmavene, Inc. has developed a multi-unit extended-release capsule formulation of carbamazepine (CARBATROL) designed to enable BID daily administration. The multi-unit is composed of three types of pellet, with each pellet type combined in a specific ratio within one capsule. The three types of pellet consist of immediate-release, sustained release and enteric-release pellets. The ratios of the immediate release, sustained-release, and enteric-release pellets are identical for each dosage strength capsule. See below:

Dosage Strength	*% of pellets within each CBZ extended-release Capsule*		
	Immediate Release	Sustained Release	Enteric Release
200 mg capsule	- -		
300 mg capsule			

The sponsor is relying upon the finding of bioequivalence to the approved immediate release formulation of Tegretol for approval of its claim for efficacy. Pharmavene, Inc. has invoked the regulations, section **21CFR§505(b)(2)** and has referenced **NDA 16-608** for all relevant data regarding the drug substance which is the active ingredient in this formulation. In addition, the sponsor has performed one clinical trial in its development program in support of its claim for efficacy.

[1] The extended release formulation of Tegretol (carbamazepine) has recently been approved in the form of Tegretol XR (CIBA Geigy).

1.0 Materials Utilized in Review

1.1 NDA

The following table lists the specific volumes that were examined in reviewing this NDA. A traditional approach to safety and efficacy was not taken by the sponsor because this NDA relied primarily on the finding of bioequivalence to the currently marketed immediate release tablet given q6h.

Table of NDA Volumes Reviewed for Clinical Evaluation of Carbatrol

Category	*Study*	*Date received*	*Volume*
Efficacy	ISE (brief summary)	4/3/1996	1.24
	Study 101.104	4/3/1996	1.26
Safety	ISS (2 page summary)	4/3/1996	1.24
	4M Safety Update	10/3/1996	5.1
	Safety Study 101.103	4/3/1996	1.24-.25
	Study 101.104	4/3/1996	1.26
	Study 101.104a	4/3/1996	1.27
	Study 101.106	4/3/1996	1.28
	CRFs of WDAE	4/3/1996	1.41
Biopharmaceutical	Summary of Biopharmaceutical Data	4/3/1996	1.1
	Study 101.103	4/3/1996	1.24-1.25
Draft Labeling	First Draft Labeling	4/3/1996	1.29
	Revised Draft Labeling	12/29/1996	6.1

1.2 Material from IND

The sponsor references materials submitted to the IND regarding toxicity of the Eudragit family of compounds (August 11, 1994 IND serial no. 016).

1.1 Published literature

There is no published literature specifically on this product.

2.0 Background

2.1 Indication

Carbatrol was developed to be bioequivalent to carbamazepine, and therefore the indications proposed for its use are the same as those of carbamazepine:

Epilepsy:

Partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic-clonic seizures, and mixed seizure patterns which include the above, or other partial or generalized seizures.

Trigeminal Neuralgia:

Pain associated with trigeminal neuralgia. Beneficial results are also reported with glossopharyngeal neuralgia.

2.2 Related INDs and NDAs

This application bears some similarity to the recently approved product Tegretol XR (NDA #20-234) which was submitted for approval based on bioequivalence to the currently marketed immediate release Tegretol. It is important to recall the basis for that approval in considering the current application for the sake of consistency, since the same issues potentially apply.

In the Tegretol XR application, data or support from the literature illustrating the importance or lack of importance of rate of delivery of drug was requested of the sponsor, or alternatively, a clinical trial to establish that the rate of absorption was not important for clinical efficacy. To this end the sponsor undertook to perform an animal study (alumina gel monkey model for epilepsy) intending to demonstrate that the rate of Tegretol delivery does not affect its efficacy. The study failed to provide such evidence, and the FDA was left to rely upon biopharmaceutical data in its deliberations. It should be pointed out that this study was not designed to address the question of safety given a formulation which potentially had less extreme C_{min}'s and C_{max}'s than the immediate release compound but rather a more constant plasma level chronically. The product also failed strict bioequivalence standards but was approved based on two assumptions which will be summarized below.

The first assumption which led to the ultimate approval of Tegretol XR was that the 10,11-epoxide metabolite which has been shown to be an active species in animal models of epilepsy should not be ignored in decisions of bioequivalence where the parent compound passes but the epoxide fails (even by a small margin) since the epoxide is thought to be just as potent in humans. This was the case with Tegretol XR, however, the products were found to produce bioequivalent amounts of active anticonvulsant species when the parent compound and active metabolite (CBZ-10,11-epoxide) were considered additively (See Dr. Paul Leber's memo to file NDA #20-234, dated 3/22/1996). The rationale for this was that the 10,11-epoxide metabolite is equipotent in animal studies in the prevention of epileptic seizures. Such an assumption cannot be extrapolated to trigeminal neuralgia and would apply only to the epilepsy indication.

The second assumption that was made which led to the ultimate approval of Tegretol XR was that it had been demonstrated from a previous study of valproate (1989 approval of Depakote sprinkles) in the same animal model alluded to above that the rate of infusion of the anticonvulsant did not adversely affect the efficacy of valproate in that model. The depakote labeling included the following language that was a reflection of the thinking that went into the valproate thinking process, which also applies to this current application.

> Equivalent oral doses of Depakote (divalproex sodium) products and DEPAKENE (valproic acid) capsules deliver equivalent quantities of valproic ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle),conditions of use (e.g., fasting or postprandial) and the method of administration (e.g., whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy.
>
> However, it is possible that differences among the various valproate products in Tmax and Cmax could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate of absorption of the tablet (increase in Tmax from 4 to 8hours) than on the absorption of the sprinkle capsules (increase in Tmax from 3.3 to 4.8 hours).
>
> While the absorption rate from the G.I. tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint.[2]

It was presumed in the case of the above approval that rate of administration of an anticonvulsant given chronically or the degree of fluctuations in plasma levels does not adversely impact its efficacy as an antiepileptic as long as the extent of absorption was equivalent to the approved product. This presumption was similarly applied to the Tegretol XR application in its approval. Because this policy was not in place when discussions with Pharmavene, Inc. were held, the advice to the sponsor was to undertake to evaluate this issue with animal and/or clinical trials. The sponsor has indeed provided one animal study and one clinical study to address the issue of efficacy.

All of the above deliberations addressed the potential efficacy of the drugs in question, but did not in any substantive way address the issue of safety. The controlled release product was assumed to be as safe as the immediate release product because the fluctuations of Tegretol plasma levels from the XR formulation were less than those measured in the immediate release formulation and because the Cmax's were relatively lower. This assumption may be correct. If the controlled release product had resulted in reduced overall fluctuation but higher Cmin's one could argue that the more constant carbamazepine exposure with overall higher Cmins may result in increased risk to the patient. However with Tegretol XR

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[2] Approved labeling for Depakote tablets

it was the case that the Cmins were actually slightly lower than in the IR product. This formulation of carbamazepine produces slightly different kinetics and this will be summarized in section 6.0 and discussed fully in the Biopharmaceutics Review by Dr. Mahmood.

2.1 Administrative History

- IND Submitted to FDA—January 31, 1992
- Teleconference with Sponsor to discuss development plans—May 29, 1992
- Meeting with Epilepsy Branch Advisory Committee on AEDs (February 23, 1993) Recommendation made by FDA that Pharmavene explore the effects of the dosing regimen of Carbamazepine in an experimental model of Epilepsy.
- IND November 19, 1993—(IND serial 013): Materials submitted to FDA to explore efficacy in the setting of altered dosing regimen.
- End of Phase 2 meeting January 19, 1994
- Pre-NDA meeting—February 1, 1996
- NDA filed April 3, 1996
- Safety Update filed 10-3-1996

2.1 Directions for Use (proposed)

"Carbatrol is a controlled-release formulation for twice a day [oral] administration. When converting patients from immediate release Tegretol® (carbamazepine) to Carbatrol controlled-release capsules, the same total daily mg dose of carbamazepine should be administered.

Children over 12 years of age. Initial: 200 mg twice daily. Increase at weekly intervals by adding up to 200 mg/day until the optimal response is obtained. Dosage generally should not exceed 1000 mg per day in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults. **Maintenance:** Adjust dosage to the minimum effective level.

Children under 12 years of age Children taking total daily dosages of immediate release carbamazepine of 400 mg or greater, may be converted to the same total daily dosage of Carbatrol controlled-release capsules, using a twice daily regimen.

Combination Therapy: Carbatrol may be used alone or in combination with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased.

Trigeminal Neuralgia:
Initial: On the first day, start with one 200 mg capsule. This daily dose may be increased up to 200 mg/day every 12 hours only as needed to achieve freedom from

pain. Do no exceed 1200 mg daily. **Maintenance:** Control of pain can be maintained in most patients with 400-800 mg daily. However some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily.

2.5 Foreign Marketing

Carbatrol had not been approved for marketing in any other country as of the date of this submission.

3.0 Chemistry

Carbamazepine is an imunostilbene and a structural congener of the tricyclic antidepressant imipramine. Carbamazepine used in the manufacture of Carbatrol is manufactured by

- Molecular weight: 236.27
- White to off-white powder
- Hydrophobic drug—almost insoluble in water
- Soluble in alcohol

Carbatrol is a three-component formulation of carbamazepine composed of an immediate release, sustained release and enteric release dosage form. The three components are combined in specific ratios within one capsule to produce a multi-unit sustained release formulation of carbamazepine. The sustained release and enteric-coated release pellets are made by coating the immediately release pellets with sustained release and enteric release coatings. The pellets are filled using of the Immediate release, sustained-release, and enteric release pellets, respectively to form the composite dosage form. The extended release capsules come in two dosage forms, 200 and 300 mg which contain the components described above in exactly the same ratio.

The composition of the sustained-release and enteric-release coatings are detailed by the sponsor and include triethyl citrate, colloidal silicon dioxide. is the trade name for a family of pharmaceutical

Chemistry deficiencies include EA and inspection problems of which the sponsor has been notified.

4.0 Animal Pharmacology

4.1 Mechanism of Action

While the sponsor has referenced NDA 16-608 and the mechanism of action reported for Tegretol applies here, the sponsor has undertaken an additional burden, that is, to explore the effect of the dosing regimen of carbamazepine on efficacy in an experimental animal model.

Dr. Harold H. Wolf, PhD of the University of Utah conducted a study on the anticonvulsant efficacy of carbamazepine as a function of dosing frequency.[3] The study examined the effect of plasma fluctuations in plasma levels of carbamazepine were necessary for the drug's therapeutic efficacy in the treatment of seizures.

Design: A group of 40 rats were treated with frequent low dose carbamazepine (to simulate plasma levels at steady state) and another group received the same TDD of carbamazepine as higher, less frequent doses (simulating fluctuating levels). Their response to MES induced convulsions was monitored.

Results: The study found that 40 rats in the "fluctuating level" group and 38 rats in the "steady level" group were protected against MES convulsions. The difference between the two groups was not statistically significant.

Conclusion: The sponsor has concluded from this study that fluctuating and steady levels of carbamazepine are pharmacodynamically equivalent in the prevention of seizures.

Please refer to Dr. Edward Fisher's review of the preclinical pharmacology-toxicology for a full discussion of these materials.

4.2 ADME

The sponsor references the innovator NDA #16-608 for these materials.

4.3 Preclinical Toxicology

The sponsor has not conducted any studies to explore the toxicology of th

[3] The results of this study were previously submitted to the IND (November 19, 1993—IND serial 013) and were presented to the FDA at the End of Phase 2 meeting on January 19, 1994.

The sponsor has alluded to other examples of chronic daily administration of Drug Products containing which would be expected to deliver more of the substance than Carbatrol does. However no comparative numbers were supplied.

Comment: Clearly chronic human exposure data are more relevant than any animal toxicity data that the firm could provide the FDA at this time. These examples, albeit few, where doses exceeding the expected total daily dose on a chronic (years) basis from Carbatrol provide some assurance of the safety of this compound in humans.

5.0 Description of Clinical Data Sources

5.1 Primary Source Data (Development Program)

A total of 14 human studies were submitted to this 505(b)(2) application. Eleven of these were Clinical Pharmacology studies , and there were also two clinical safety trials and one double blind efficacy study.

5.1.1 Study Type and Design/Patient Enumeration

The table below shows the distribution of patients across treatment groups for each study pool as of the cutoff date for the 4 month Safety Update to the NDA which was 8-31-1996. An additional 24 patients in ongoing phase 2-3 trials were added to this safety data base with the submission of the Safety Update on 10-3-1996 for a total of 357 exposures.

Table 1.1
Number of Subjects/Patients for Carbatrol Development Program (cutoff date: 8-31-96)[a]

Study Groups	Treatment Groups		
	New Drug	Active Control	
	Carbatrol	*Tegretol*	*Depakote*
Completed Phase 1[b]			
Single Dose			
formulation study	43	12	0
pharmacokinetic study	73	0	0
Phase 1 Subtotal	116	12	0
Completed Phase 2-3[c]			
Active Control			
Fixed Multiple Dose	145[e]	25	55
Phase 2-3 Subtotal	145	25	55
Ongoing Phase 2-3[d]			
Uncontrolled			
Long Term (6 month)			
in original NDA	72	0	0
in 4-month Safety Update	24	0	0
Ongoing Phase 2-3 Subtotal	96	0	0
Single Dose Subtotal	116	12	0
Multiple Dose Subtotal	241	25	55
Grand Total	357	27	55

[a] This was the cutoff date of the 4-month safety update; and the cutoff date of the original NDA#20712 was 2-29-96;

[b] Including studies of PI 101.101/101b/101c/102 for formulation study and PI 101.107/108/109/110/112/113 for pharmacokinetic study;

[c] Including studies of PI 101.103/104(104a);

[d] Including study of PI 101.106;

[e] Including 62 patients who were assigned to depakote group in PI 101.104 study; but, they received Carbatrol treatment for the first 4 weeks per study design. Among the 62 patients, 55 received the assigned Depakote treatment after the first 4 weeks in the study.

5.1.1 Demographics

Baseline demographic characteristics are shown below in Sponsor's Table 1.2 for age, gender and race for patients enrolled in phase 1 , 2 and 3 studies. Individuals enrolled in phase 1 single dose studies were normal healthy subjects. Individuals enrolled in phase 2-3 studies (and in phase 1 multiple dose studies) were patients with partial complex seizures

Table 1.2
Demographics Profile for Phase 1 & 2-3 Studies with Carbatrol
(cutoff date: 8-31-96)[a]

Demographic Parameters	Phase 1[b] Treatment Groups		Phase 2-3[c] Treatment Groups		
	New Drug	Active Control	New Drug	Active Control	
	Carbatrol	*Tegretol*	*Carbatrol*	*Tegretol*	*Depakote*
	N = 116	N = 12	N = 241	N = 25	N = 55
Age (years)					
Mean	32	27	34	36	34
S.D.	8	5	10	8	9
Range					
Group					
< 40	79%	100%	71%	64%	72%
40 - 64	21%	0%	28%	36%	27%
> 64	0%	0%	1%	0%	0%
Sex					
Female	1%	0%	56%	56%	51%
Male	99%	100%	44%	44%	49%
Race					
Caucasian	92%	92%	93%	68%	100%
Non-Caucasian	8%	8%	7%	32%	0%
Weight (lb)					
Mean	172	176	158[d]	167[d]	143
S.D.	22	19	36	36	26
Range					

[a] This was the cutoff date of the 4-month safety update; and the cutoff date of the original NDA#20-712 was 02-29-96;

[b] Including studies of PI 101.101/101b/101c/102 for formulation study and PI 101.107/108/109/110/112/113 for pharmacokinetic study;

[c] Including studies of PI 101.103/104(104a)/106(in original NDA and 4-month safety update);

[d] Weight was missing for one patient.

5.1.3 Extent of Exposure (dose/duration)

The next table shows exposure to Carbatrol by dose of patients in all studies.

Dose Exposures of Study Participants in PI 101 Studies of Carbatrol

Dose (mg)	*Single Dose*		*Multiple Doses*			*Total*
	Carbatrol	Tegretol	Carbatrol	Depakote	Tegretol	Carbatrol
200 mg	11	-	-	-	-	11
300 mg	35	-	-	-	-	35
400 mg	219	12	3	-	-	222
500 mg	12	-	-	-	-	12
600 mg	36	-	8	-	-	44
700 mg	-	-	7	-	-	7
800 mg	12	-	120	28	10	132
900 mg	-	-	3	-	-	3
1000 mg	-	-	9	-	-	9
1100 mg	-	-	1	-	-	1
1200 mg	-	-	73	19	9	73
1300 mg	-	-	1	-	-	1
1400 mg	-	-	4	-	-	4
1500 mg	-	-	1	-	-	1
1600 mg	-	-	31	8	6	31
1700 mg	-	-	2	-	-	2
1800 mg	-	-	2	-	-	2

The table below shows the exposure to Carbatrol in patients in Phase 2-3 studies by duration of treatment.

No of Patients in Continuous Exposure to Carbatrol During Multiple Dose Studies

No of Weeks	Carbatrol
2 weeks	231
4 weeks	200
12 weeks	135
24 weeks	117

The next table shows the exposure to Carbatrol in clinical studies by dose and duration of exposure.

Table 1.3
Number (%) of Patients Receiving Study Medication According to Mean Daily Dose and Duration of Therapy in Phase 2-3 Studies[a]
(cutoff date: 8-31-96)[b]

Duration[c] (weeks)	Mean Daily Dose (mg)						
	100<=Dose<=400	400<Dose<=800	800<Dose<=1200	1200<Dose<=1600	1600<Dose<=1800	Total	(%)
	Carbatrol (N=241)						
0 < Duration <= 1	0	4	1	1	0	6	2%
1 < Duration <= 2	0	10	10	8	0	28	12%
2 < Duration <= 4	0	22	19	10	0	51	21%
4 < Duration <= 12	0	9	6	4	1	20	8%
12 < Duration <= 23	0	11	7	2	1	21	9%
24 <= Duration <= 26	4	62	36	13	0	115	48%
Total	4	118	79	38	2	241	100%
(%)	1%	50%	33%	16%	0%	100%	
	Tegretol (N=25)						
0 < Duration <= 1	0	0	0	0	0	0	0%
1 < Duration <= 2	0	10	9	6	0	25	100%
Total	0	10	9	6	0	25	100%
(%)	0%	40%	36%	24%	0%	100%	
	Depakote (N=55)						
0 < Duration <= 1	0	4	3	2	0	9	16%
1 < Duration <= 2	0	1	1	1	0	3	5%
2 < Duration <= 4	0	7	3	3	0	13	24%
4 < Duration <= 12	0	16	12	2	0	30	55%
Total	0	28	19	8	0	55	100%
(%)	0%	51%	35%	14%	0%	100%	

[a] Including studies of PI 101.103/104(104a)/106(in original NDA and 4-month safety update);
[b] This was the cutoff date of the 4-month safety update; and the cutoff date of the original NDA#20-712 was 02-29-96;
[c] Calculated based on the smallest time unit available from each of those studies mentioned above.

5.2 Secondary Source Data

Not applicable

5.3 Comment on Adequacy of Clinical Experience

As a 505(b)(2) submission, based on a finding of bioequivalency with marketed carbamazepine (Tegretol) there is little concern for new information about the safety and efficacy of this product. The development plan conducted over the past five years with occasional guidance from the Division has been adequate from a clinical standpoint.

6.0 Human Pharmacology

This section will summarize the main points of human pharmacology pertaining to this 505(b)(2) application designed to demonstrate bioequivalence with Tegretol tablets as labeled. For a complete review of these data and for the specific bioequivalency analyses, please refer to Division of Biopharmaceutics review by Dr. Iftekhar Mahmood. The major points are summarized below:

Conclusions of Biopharmaceutics Reviewer:

- Carbatrol given BID is bioequivalent to Tegretol administered on a QID schedule.
- Carbatrol 200 mg TID is equivalent to Carbatrol 300 mg BID
- Carbatrol is equally bioavailable when administered fasting or with food
- Carbatrol capsules produced before and after 1993 are bioequivalent

The Pharmacokinetics studies performed by the sponsor are enumerated in the table below for reference.

PHARMACOKINETICS STUDIES	**PROTOCOL NUMBER**
Pilot/exploratory formulation studies in healthy volunteers	101.101 (a); 101.101 (b); 101.101 (c); 101.102
Multiple dose bioequivalence studies vs Tegretol (patients)	**101.103**
Single dose Pharmacokinetics studies (healthy volunteers)	101.107; 101.108; 101.109; 101.110; 101.112; 101.113

Of the studies listed above, four were pilot studies or early pharmacokinetics studies in normal healthy volunteers undertaken to finalize the pellet formulation. In each of these studies, each type of pellet was encapsulated separately so that the bioavailability of each could be separately assessed. Once each pellet was separately characterized the pellets were combined in order to produce the desired pharmacokinetic profile in the form of Carbatrol.

The next study (101.103) was a multiple dose study in patients to assess the bioequivalence of Carbatrol given BID with the same TDD of Tegretol given QID. The batch used in the pivotal bioequivalence study (produced in 1993) was manufactured by a different process than batches subsequently produced (1994 and 1995). Therefore a study demonstrating a pharmacokinetic "link" between these two batches demonstrating dose equivalence was done (101.112). Five additional studies were performed in order to assess dose proportionality, bioavailability of different batches, equivalency of different formulations (200 and 300 mg capsules), dose equivalency (comparing 2x300mg and 3x200mg), and effect of food.

In the pivotal biopharmaceutics study of this NDA, **Study 101.103** the sponsor demonstrated bioequivalence between CBZ-SR (Carbatrol) administered BID and Tegretol administered 4 times daily. In this study 24 patients with epilepsy (maintained on carbamazepine monotherapy or adjunctive therapy) received a TDD of Tegretol 800 mg (N=9), 1200 mg (N=6) Carbatrol or Tegretol IR for 14 days. Tegretol IR was given every 6 hours and CBZ-SR was given every 12 hours.

Results:

The results of the pharmacokinetic analysis were determined from 1) *summation* of CBZ *plus* CBZE (epoxide metabolite) concentrations in the plasma, 2) plasma CBZ levels and 3) plasma CBZE levels. Mean values were obtained for AUC, C_{max}, C_{min}, Cavg , and t_{max} following the administration of Carbatrol and Tegretol and were compared for all patients combined across dosage groups. Fluctuation index (I) was calculated from Cmax-Cmin/Cavg for all three time intervals (0-12, 12-24 and 0-24hours) and were compared for all patients combined . The results are summarized in the Sponsor's Tables1.1 for CBZ+CBZE, CBZ and CBZE. (attachment 1). Note that all dosage groups for a given treatment were combined for comparison. This was specified in the protocol. The various dosage groups corresponded to the dosage of carbamazepine on which the patients had been maintained or controlled prior to randomization. These were not intended as strata for purposes of subgroup analysis by dosage level.

As shown in tables 1.1 (three pages) for the parent species (CBZ) and the summation of parent and epoxide metabolite (CBZ+CBZE) all pharmacokinetic parameters, namely AUC, Cmax, Cmin, and Cavg satisfy the recommended 90% confidence limits for bioequivalence (.80-1.25) on the log transformed levels. As in the case of Tegretol XR, the 90% confidence intervals on the log transformed epoxide levels alone fail by a small margin for Cmin and Cmax. AUC and Cavg are all within the recommended range.

The FI for was slightly higher in the CBZ SR product compared to Tegretol IR and the confidence were slightly outside of the upper recommended limits (see table 1.1) for the CBZ and CBZE (not calculated for CBZ plus CBZE).

The tmax was evaluated as well. The sponsor maintains that in a multiple dose study in which the PK data were evaluated on day 14, the tmax may have little meaning. Nevertheless they were obtained (attachment 2) for CBZ and CBZE. There was not statistical difference between the Tmax at any of the time periods or at any of the doses administered. Confidence intervals were not calculated for this parameter.

The bioeuqivalence parameters were calculated for each of the three dosage groups in this study (800,1200, and 1600 mg) by FDA biopharmaceutical consultant, Dr. Mahmood. In all cases, as expected by the small sample size of these subgroups, bioequivalence failed. This was considered a power issue both by the sponsor and FDA biopharmaceutics reviewers. It was not an intended analysis.

Reviewer's Comment: As previously established policy for antiepileptic drug products in the cases of the Depakote Sprinkles (1989) and Tegretol XR (1995) approvals, the fluctuation index has not been considered as critical in the determination of therapeutic equivalence as the AUCs. No new information is available that would call that policy into question.

The recommended criteria for bioequivalence have been met for the parent drug (CBZ) but not the metabolite (CBZE) at all dosage groups for AUC, Cmax and Cmin, similar to the pattern seen with Tegretol XR. Parent plus epoxide satisfy the same criteria used for Tegretol XR.

7.0 Summary of Efficacy

The sponsor has submitted one human study in support of the finding of efficacy demonstrated in Study 101.104.

7.1 Study 101.104

TITLE: Multi-dose Evaluation of Safety and Efficacy of a Multi-Unit Dose of Carbamazepine in Epileptic Patients

OBJECTIVE: to evaluate the efficacy and safety of the multiple-unit, sustained release dosage form of carbamazepine compared to a sustained release formulation of valproate sodium (Depakote).

STUDY DESIGN: Active control randomized parallel group study comparing Carbamazepine-SR (Carbatrol) with Depakote.

PROTOCOL: This was a 12-week multicenter (4 sites), outpatient, randomized double-blind, parallel group active-control trial in patients with complex partial seizures. Projected enrollment included 4 centers of 25 patients each for a total of 100 patients. Patients would be enrolled who had been maintained on stable regimen of antiepileptic drugs which included carbamazepine monotherapy or carbamazepine plus one additional antiepileptic drug product excluding valproate.

Inclusion Criteria:

- Males and females 18-60
- Ideal weight for height within 10-25%
- History of partial seizures with complex symptomatology with or without secondary generalization
- History of at least 2 seizures in the 4 weeks prior to their entry into the study
- Stable regimen of carbamazepine at least 30 days prior to enrollment. (During the first 4 weeks after enrollment patients must receive a fixed daily dose of carbamazepine equal to 800, 1200, or 1600 mg.
- Patients may receive one additional AED (not valproic acid) as long as doses remain stable for at least 30 days prior to study entry
- Physically healthy for their age with no history of chronic or debilitating illness
- Compliant and having signed informed consent

Exclusion Criteria:

- History of sensitivity or adverse reaction to carbamazepine, valproic acid, or tricyclic antidepressants
- Significant history of heart disease, MI within 6 months; history of uncontrolled hypertension, abnormal BP (defined by >160/110 or <80/60); pulse >100 or <60/min.
- History of psychiatric or neurological disorder (other than epilepsy)
- Requirement of chronic medications which may interfere with compliance or study conduct
- Abnormal labs
- Use of investigational drugs within 4 weeks, use of drug with known well-defined potential for toxicity to a major organ system within a month of entering the study
- Chronic disease of GI tract, liver, kidneys or abnormal condition that compromises the function of these systems resulting in altered absorption, excess accumulation, or impaired metabolism or excretion of the study drug
- Substance abusers
- Pregnancy or lactation (Females who are premenopausal must have a negative pregnancy test and be practicing an effective method of birth control).

Study Schedule:

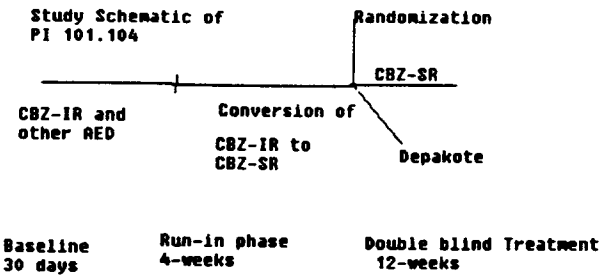
Pre Entry Period: Once admission criteria are established for patient eligibility, the patient would undergo physical examination, including height and weight, complete medical history, and routine clinical laboratory evaluation. Patients desiring to enroll in the study would have their dose adjusted to 800, 1200 or 1600 mg (depending on their current maintenance dose) either immediately or one week prior to study entry.

According to the protocol, patients would have their daily fixed dose of carbamazepine as **Carbatrol** given q12 hours and continue to receive their second AED for the first 4 weeks of the study. They would then be randomized to receive either Carbatrol q12 hours (Treatment 1) or valproic acid (Treatment 2) q12 hours. Patients would receive these medications according the schedule below:

Assignment	wks 1-2	wks 3-4	wks 5-6	wks 7-8
800 mg CBZ dose				
carbamazepine	2 CBZ bid	2 CBZ bid	2 CBZ bid	2 CBZ bid
valproic acid	1 VAL + 1 CBZ bid	2 VAL bid	2 VAL bid	2 VAL bid
1200 mg CBZ dose				
carbamazepine	3 CBZ bid	3 CBZ bid	3 CBZ bid	3 CBZ bid
valproic acid	1 VAL + 2 CBZ	2 VAL + 1 CBZ bid	3 VAL bid	3 VAL bid
1600 mg CBZ dose				
carbamazepine	4 CBZ bid	4 CBZ bid	4 CBZ bid	4 CBZ bid
valproic acid	1 VAL + 3 CBZ	2 VAL + 2 CBZ	3 VAL + 1 CBZ	4 VAL bid

The schedule for conversion of Carbatrol to Depakote ranges from 3 weeks in the low dose group (500 mg) to 8 weeks in the case of patients in the higher dose group (1000 mg). The dosage assigned to patients corresponds to the dose of carbamazepine on which they entered the study. In other words, patients who entered the study on 800 mg of carbamazepine were randomized to either 800 mg Carbatrol or 250 mg Valproate; patients who entered the study on 1200 mg of carbamazepine were randomized to either 1200 mg of Carbatrol or 750 mg of valproate; and patients who entered the study on 1600 mg of carbamazepine were randomized to either 1600 mg of Carbatrol or 1000 mg of valproate. The final analyses did not take this stratification into account, but rather pooled all Carbatrol

treated patients and compared them to all valproate treated patients. The study schematic is summarized below.



Efficacy Criteria

Efficacy was to be assessed by

1) Number of patients completing the study who failed to meet escape criteria
2) Time to drop-out including those patients who remain in the study

Proposed Analysis

Proposed analysis was in two parts:

1. Background Information

This entails comparison of the two groups of treatment: CBZ SR and VPA with respect to the patient's demographic and physical characteristics, seizure frequency, adverse reactions and lab tests. Each variable will be analyzed across centers and within each treatment center.

2. Efficacy of CBZ SR formulation

Escape Criteria

a. Twofold increase in highest 2-day seizure frequency or two seizures in a week for patients who had not seizures during the 4-week run-in period
b. Twofold increase in weekly seizure frequency (complex partial or secondarily generalized seizures), or two seizures in two weeks in patients who had no seizures during the 4-week run-in period
c. A single GTC seizure if GTC seizures were not present during the 4-week run-in period
d. A prolongation of generalized seizure duration (serial seizures or status) deemed by the investigator to require intervention.

First: The percentage of patients meeting the escape criteria (or completed the entire study will be compared using the Corchoran Manetl-Haenzel test or Chi Square test, respectively for the analysis with and without controlling the effect of treatment center.

Second: The time (in days) of the patient's remaining in treatment until escaping from or completing therapy (survival time). The hazard function estimates will be plotted against the time variable for the six combinations of treatment group by dose level, respectively, to examine by visual inspection if there exists any undesirable interaction between the two treatments. Survival

curves of the treatment groups will be compared using the log rank test and the Wilcoxon test. The dependence of survival time on the treatment group variable will be assessed while adjusting for the treatment center and/or any other relevant variables. If the observed data satisfy the proportional hazards assumption, the Cox regression model will be used to examine the hazard ratio between the two treatment groups.

STUDY CONDUCT The study was conducted in Poland. Four centers participated in this study. A total of 121 patients were randomized, 59 to CBZ-SR and 62 to Depakote. Study conduct proceeded according to the protocol.

During the first 4 weeks of the study ("run-in" period) all patients received their established fixed daily dose of carbamazepine as CBZ-SR q 12 hours regardless of their randomization[4]. In addition, they received their concomitant AED (not VPA). During this period, carbamazepine levels were measured.

After 4 weeks patients were randomized to receive either CBZ-SR q12 hours (treatment 1) as well as their additional AED or Depakote (treatment 2) q12 hours for up to 8 weeks. The maximum daily dose of CBZ-SR was 1600 mg and the maximum daily dose of Depakote was 1000 mg/day. All doses were determined by the TDD of carbamazepine with which the patient entered the study. (see table). The length of investigation was up to 84 days (12 weeks) for each subject.

Patient Disposition

	CBZ-SR	Depakote
Entered	59	62
Completed	38	12
Discontinued	21	50
Assessed for Efficacy	59	62

The study was conducted according to protocol. There were no significant violations that would affect the outcome of the study. Evaluation of baseline comparability between the treatment groups yielded no disparities between the two groups with regard to demographics (age, sex, height and weight), diagnosis, use of a second anticonvulsant, carbamazepine dosage, and years of epilepsy.

SPONSOR'S RESULTS:

The primary outcome measure for this study was a comparison of the percentage of patients meeting the escape criteria or completed the entire study using the CMH test or Chi Square test. The sponsor's results shown below do demonstrate a statistically significant difference between the number of completers in the CBZ-SR group compared to the Depakote group.

Comparisons of Study Completion by Assignment for all Patients:

[4]Up to one week before the study began patients could have their dose adjusted to one of the fixed daily doses.

Intent to Treat Analysis

	CBZ-SR N (%)	Depakote N(%)	Significance (p-value)
Percentage completing study (N=121)	38 (64.3)	12 (19.4)	0.001* 0.001**

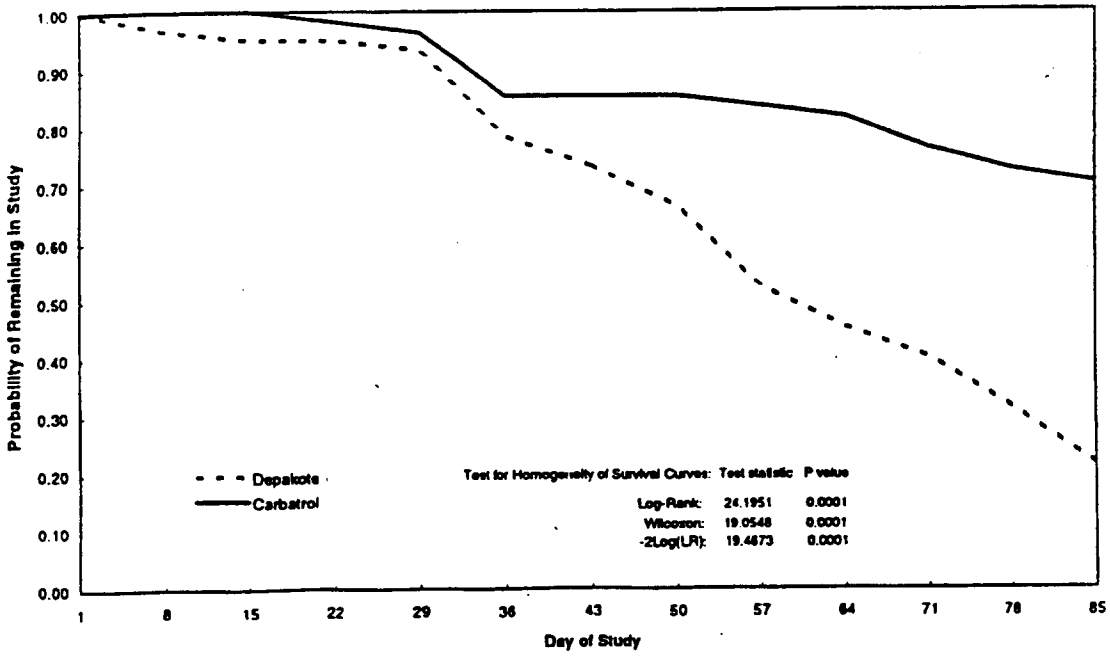
*Chi-Square p=0.001
Mantel-Haenzel p=0.001

There was no attempt to look at the performances within the low, medium and high dose strata and this was not planned in the protocol.

The secondary outcome measure was the time (in days) of the patient's remaining in treatment until escaping from or completing therapy (survival time). Sponsor's Figure 1.1a (see attachment 4) presents the survival function for the 12-week long study period, including all 121 randomized patients. All three tests for homogeneity of the survival curves(Log-rank, Wilcoxon, and likelihood ratio) confirmed significant differences between treatments (all doses of CBZ-SR vs all doses of Depakote), favoring CBZ-SR (p=0.0001).

The weekly hazard rate estimates (chance of being terminated from the study) were presented graphically in sponsor's Figure 1.2 for the entire 121 patient group. The hazard rate estimate for Depakote exceeded that for every week during the randomized treatment period. One could argue, however that for the Depakote group only titration off carbamazepine was an every other week occurrence and may have introduced the potential variable of withdrawal seizures. Figure 1.2 is found in attachment 4.

Figure 1.1 Survival Function for the 12-Week Study Period (N=121)



FDA COMMENTS:

The study demonstrated clearly that there is a difference between carbamazepine SR and Depakote in the prevention of seizures. The context of this study, however, was in the withdrawal of patients from Carbamazepine IR. Withdrawal from Carbamazepine IR was associated with worsening of seizures (as defined by escape cirteria) in both treatment groups, but clearly much more so than in the low dose Depakote group(statistically significant). However, the survival curves presented by the sponsor in Figure 1.1 also demonstrate a slight fall off in "survival" of patients on Carbatrol compared to baseline. (approximately 70% remaining at day 85), indicating that some patients needed to "escape" from the study because of increased seizures. In the absence of a control group (patients who did not undergo change to Carbamazepine SR from IR) there is not means of interpreting this trend. The decline in seizure control may be attributable to the natural history of the disorder in those patients or it could be due to the change in regimen. Without a control group no conclusions can be drawn. The study fails to provide the supportive evidence for carbamazepine IR's and Carbatrol's therapeutic equivalence.

The study is supportive of the efficacy of Carbamazepine SR compared to low dose Depakote in the prevention of seizures occurring after withdrawal of parent drug. However, this alone cannot necessarily be considered an unequivocal demonstration of efficacy in the setting of spontaneous seizures. Such evidence is not really required in this context, however. The biopharmaceutical data demonstrate that the sustained release carbamazepine is bioequivalent to the current marketed immediate release product administered on a QID schedule. The request for approval for marketing is based on the demonstration of bioequivalene and the biopharmaceutical data are adequate and compelling.

If the biopharmaceutical data were equivocal or negative, then further studies would be required for approval. In view of the fact that this study alone was not capable of demonstrating the efficacy of Carbatrol in the prevention of partial onset seizures, it was not considered necessary for a formal biostatistical analysis to be obtained at this time. No special analyses were considered necessary, and the sponsor's results in this study were accepted on face value..

8.0 Integrated Review of Safety

8.1 Background and Methodology for Safety Review

The firm asserts that the safety of carbamazepine was established by NDA 16-608 (Tegretol tablets) and submits the prior evidence for support of this application through reference to that NDA (NDA #20-712 volume 1.24, page 43), citing §505(b)(2) of the 21CFR. The sponsor has provided as supportive data the safety experience from the Carbatrol development program. The safety data base for this NDA was small. Data from individual studies were supplied. There was no Integrated summary of Safety in the conventional sense, although integrated safety tables were provided and were reviewed.

The safety data are pooled by single dose and multiple dose experience. There were 116 volunteers in single dose studies. The demographics of this population are described in Section 5.0 of this review. The crossover design of many of the studies in this program resulted in 116 subjects receiving a total 325 doses of Carbatrol. The doses ranged from 300 mg to 800 mg. The majority of the single dose experience was at 400 mg.

The multiple dose experience is described in Section 5.0. All patients in the multiple dose studies were patients with partial onset seizures. There were no patients with trigeminal neuralgia in this data base. Multiple dose studies ranged from 400 to 1800 mg/day. With the majority receiving doses of 800 mg per day.

In evaluating the safety of Carbatrol the Carbatrol-exposed population was examined for serious adverse events and commonly collected and reported adverse events were reviewed. The case reports associated with serious adverse events and withdrawals due to adverse events were reviewed. The materials from the original NDA submission and Safety update were relied upon for this evaluation.

There are no new indications proposed in this submission that are not found in the Tegretol labeling, which includes epilepsy and trigeminal neuralgia. The population studied in this NDA, however, were normal volunteers and epileptic patients. There were no tic patients studied.

8.1.1 Deaths and Serious Adverse Events

No deaths were reported in this NDA.

As required by 21 CFR §312.32 (a) the sponsor used the term "serious to describe certain types of adverse events, such as those which led to hospitalization, cancer, life threatening illness, etc. The only serious adverse event reported in this NDA was a patient reported to have taken an intentional overdose (see section on overdose 8.1.12) of Carbatrol and was hospitalized and an individual who was hospitalized with adenocarcinoma of the liver and pancreas (see dropouts 8.1.1) after 2 months of Carbatrol therapy.

8.1.2 Dropouts and "Other Significant Adverse Events"

8.1.2.1Overall Profile of Dropouts

Discontinuations were classified according to whether they occurred because of safety (adverse events), administrative reasons (such as protocol violations) or lack of efficacy (increased seizures). The number of patients and subjects discontinuing from clinical studies is summarized in sponsor's Table H.6b.1.4.

from Sponsor's table H.6.b.1.1
Number of Participants Discontinuing Therapy in PI 101 Studies

Number (%) of

		Participants	
		Carbatrol	Tegretol
Single Dose Studies	***Description***		
No of Participants		116	12
Reasons for discontinuation			
related to Study Drug			
Safety	Laboratory test abnormalities in 109	1(0.8)	0
unrelated to study drug			
Safety	intercurrent illness (in 101b)	1(0.8)	0
Other	Protocol Violation, etc. (1 pt in 101c; 1 pt in 108)	2 (1.7)	0
Multiple Dose Trials			
A:PI101.103			
No of Participants		24	25
Reasons for discontinuation			
unrelated to study drug			
other	protocol variation, etc.	0	1 (4.0)
A:PI101.104/104a/106			
No of Participants		236	55
Reasons for discontinuation			
related to study drug			
safety	adverse event (1 patient in 106)	1(0.4)	0
lack of efficacy	met escape criteria (61 in 104;8 in 104a;2 in 106	30 (12.7)	41 (74.5)
unrelated to study drug			
safety	illness (1 pt in 104)	1(0.4)	0
other	protocol violation, etc. (9 in 104; 4 in 106)	11(4.2	2(3.6)

*participants were counted once if they received the same drug in different phases of the study

There were relatively few discontinuation from studies in the Carbatrol development program. There were occasional withdrawals due to lack of and rare discontinuations due to adverse events. These were not serious, and not unexpected from the known profile of carbamazepine. These are described below.

8.1.2.2 Adverse Events Associated with Dropout

In the single dose studies, one patient discontinued treatment because of liver function test abnormalities which occurred 8 days after receiving a third dose of Carbatrol. The abnormalities included elevations in SGPT, SGOT, alkaline phosphatase, and total bilirubin. Following the first two doses, the patient had normal LFTs. The schedule of dosing in this patient was 800mg-600 mg and 500 mg as single doses. The subject's liver functions returned to normal within 11

days. Preceding symptoms included itching and heartburn. The range of abnormalities included peak SGPT of 300, SGOT 107, alkaline phosphatase 235, total bilirubin 1.1. Viral titers were nonreactive. No further evaluation was done.

The second subject who discontinued shortly after beginning study 101.106 due to and adverse event reported as headache, abdominal pain and backache. Symptoms resolved with OTC therapy (Tylenol). Patient also had a strep throat on admission to the study.

In the multiple dose studies two patients withdrew from treatment due to safety events. One patient taking 1200 mg/day reported fatigue, sedation and mental slowing after receiving the drug for 2 weeks. The symptoms resolved without intervention. The second patient who withdrew because of adverse events reported jaundice two months after starting treatment. He was hospitalized and evaluated and found to have adenocarcinoma of the liver and pancreas. The patient was reported to have died 6 months following the discontinuation of treatment.

One patient in study 101.106 reported withdrawal due to increase in seizure activity.

None of these adverse events are unanticipated for carbamazepine.

8.1.3 Other Significant Adverse Events

There were no new significant adverse events reported in the development of this product.

8.1.4 Other Search Strategies

No correlation of adverse events with race, age or gender could be demonstrated.

8.1.5 Adverse Event Incidence Tables

There was only one multiple dose study in which a control group was used, however this was an active control study using valproate as a comparison treatment. The usual comparison tables presented for adverse events in controlled trials will not be appropriate due to the absence of a placebo control.

In the single dose studies (N=116) the most commonly reported adverse events were headache, cold symptoms, tiredness, lightheadedness, and sore throat.

Combining open label experience with the active control experience in the multiple dose trials in patients (N=241), the adverse events that were reported in >1% of patients included the following:

Adverse events with an incidence of >1% of patients reportind at least once for all multiple dose studies N=241			
Costart Term	Number of Reports	Number of Patients Reporting	% of Patients reporting
Headache	59	28	12
Asthenia	19	11	5
Dizziness	33	11	5
Diarrhea	9	9	4
Infection	11	9	4
Abdominal Pain	12	9	4
Rhinitis	19	10	4
Somnolence	12	9	4
Insomnia	7	7	3
Accidental Injury	9	8	3
Nervousness	12	7	3
Pain	8	7	3
Amblyopia*	8	5	2
Bronchitis	5	4	2
Dyspepsia	5	5	2
Nausea	9	6	2
Pharyngitis	4	4	2
Rash	7	6	2
Tremor	5	6	2
Vision Abnormal	4	4	2
Vomiting	6	6	2

*blurred vision

The data from the open label and active control trials do not reveal any unexpected adverse events that were not previously described in the Tegretol labeling.

8.1.6 Laboratory Findings

No new laboratory patterns emerged with Carbatrol which were not previously described with the commercial formulation. The most common finding in clinical laboratory evaluations was decreased white count. The lowest WBC reported was 3,400 in one patient. There were no reports of pancytopenia or aplastic anemia. Depressed white counts were also seen in the active control group treated with immediate release Tegretol.

8.1.1 Vital Signs

No unexpected adverse events affecting vital signs were reported in Carbatrol trials.

8.1.8 EKG's

No EKG's performed in the Carbatrol trials.

8.1.9 Special Studies

None.

8.1.10 Withdrawal Phenomena and Abuse Potential

There is no new information on withdrawal phenomena or abuse potential in this NDA. The innovator product is referenced by implication.

8.1.11 Human Reproduction Data

There is no new human reproduction experience reported with this product. The innovator NDA (18-608) is referenced by implication here.

8.1.12 Overdose Experience

There was one overdose of Carbatrol reported to this NDA. This involved a patient in Study 101.106, the open label safety study. The patient was a 17 year old epileptic female patient who had been maintained on Carbatrol with blood levels at trough in the range of 11.9μg/mL. In a suicide attempt the patient ingested 49x300 mg Carbatrol capsules (total dose 14.7grams). She rapidly underwent nasogastric intubation to evacuate of gastric contents. Peak carbamazepine level was 23 μg/mL and the patient was at her worst obtunded for several hours. She left the hospital with no residual effects. This experience contributes no new information to the current labeling for Tegretol. The innovator NDA (16-608) is referenced by implication here.

8.2 Review of Systems

- **General**

No previously undescribed events reported. The most commonly reported findings were drowsiness, sleepiness and headache and fatigue.

- **Cardiovascular**

No previously undescribed events reported. No serious cardiovascular events were described. There were no dropouts due to cardiovascular adverse events.

- **Dermatologic**

No previously undescribed events reported. No serious dermatologic events were described. Two patients reported minor localized rashes, not likely drug related.

- **Endocrine/Metabolic**

No previously undescribed events reported. No serious endocrine or metabolic events were described. There were no dropouts due to endocrine or metabolic adverse events.

- **GI/Hepatic**

There was one report of moderately elevated LFTs within a week of a third single dose of Carbatrol. The patient recovered with no sequelae. It is somewhat surprising that an abrupt elevation of LFTs would occur following a 500 mg single dose (ableit a somewhat higher single dose than one might normally expect to begin with in a naiive patient). The patient's evaluation was not thorough, but viral hepatitis was thought to have been ruled out. There was prompt resolution of this abnormality. There is already language in the labeling with regard to the potential for liver damage and the necessity for monitoring LFTs.

One additional patient developed asymptomatic hyperbilirubinemia (8.8) unassociated with elevated transaminases after approxmately 5 months on treatment. The patient was reportedly asymptomatic and the Polish site was able to confirm that this was a laboratory error (by a factor of 10). The patient is well.

- **Hematological**

As expected, there were occasional reports of neutropenia with Carbatrol. The small number of outliers was examined, and no severe cases of neutropenia were observed. The depressions in white count were of the magnitude expected from carbamazepine. There were no withdrawals from treatment due to low white counts or from any other hematological abnormalities.

- **GU**

No previously undescribed events reported. No serious GU events were described. There were no dropouts due to GU adverse events.

- **Neurological**

No previously undescribed events reported. More commonly reported events included migraine, vertigo, diplopia and blurred vision. These are not unanticipated. No serious

neurologic events were described. There were no dropouts due to neurologic adverse events.

- **Pulmonary**

No previously undescribed events reported. No serious pulmonary events were described. There were no dropouts due to pulmonary adverse events.

- **Psychiatric**

No previously undescribed events reported. Nervousness was reported by a small percentage of patients receiving multiple dose drug. One attempted overdose was reported and is not thought to be related to the drug. There were no dropouts due to psychiatric adverse events.

- **Renal**

No previously undescribed events reported. No serious renal events were described. There were no dropouts due to renal adverse events.

- **Rheumatological**

No previously undescribed events reported. No serious rheumatological events were described. There were no dropouts due to rheumatological adverse events.

- **Special sensory**

See neurological, diplopia and blurred vision.

9.0 Labeling Review

The labeling submitted for this product is nearly identical to the current Tegretol labeling. The only differences are in the following sections: Chemistry, Indications, Pharmacokinetics, How Supplied, Dosage and Administration.

The only section that requires comment from a clinical standpoint is the Indications. The issue of whether the NDA supports a claim for use in trigeminal neuralgia bears discussion (see Section 2.0 Background, section 2.2 Related Reviews of this review document). Since the products compared in this application (Carbatrol and Tegretol IR) were not strictly bioequivalent (note failure of FI of both the parent and metabolite) but rather, therapeutically equivalent in accordance with prior policy with regard to antiepileptic drug products, an additional claim of efficacy in trigeminal neuralgia should be not be automatically granted. The sponsor has not included this condition in its studies nor made a reasonable case for which it should be added to the indications.

10.0 Conclusions

The sponsor has adequately demonstrated the safety and efficacy of Carbatrol for the treatment of partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic-clonic seizures, and mixed seizure patterns which include

the above, or other partial or generalized seizures based on therapeutic bioequivalence to Tegretol IR given on a QID schedule with supportive evidence of efficacy from one clinical trial and one animal study.

Support for the safety of this product comes both from a data base of 357 subjects, 117 whom have received the product for 6 months and also from accumulated years of pre and post marketing experience with Tegretol IR (assumed by bioequivalence).

11.0 Recommendations

Carbatrol should be approved for the treatment of partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic-clonic seizures, and mixed seizure patterns which include the above, or other partial or generalized seizures.

Attachment 1 (3 pages)
Sponsor's Table 1.1

Table 1.1 < PI 101.103 > Bioequivalence Analysis for CBZ plus CBZ-epoxide calculated in ug/mL: Total (all patients)
-- ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	265.400	284.179	93.8	0.93	(0.88 - 0.98)*
AUC (0-12 hr)	134.900	143.400	95.0	0.94	(0.88 - 1.00)*
AUC (12-24 hr)	130.500	140.787	93.0	0.92	(0.87 - 0.97)*
C max (0-24 hr)	13.342	14.162	95.6	0.94	(0.89 - 1.00)*
C max (0-12 hr)	13.009	13.801	95.4	0.94	(0.88 - 1.00)*
C max (12-24 hr)	12.411	13.351	93.9	0.93	(0.87 - 0.98)*
C min (0-24 hr)	8.950	9.938	90.4	0.89	(0.83 - 0.95)*
C min (0-12 hr)	9.516	10.439	92.6	0.90	(0.83 - 0.98)*
C min (12-24 hr)	9.313	10.416	89.9	0.88	(0.83 - 0.94)*
C avg (0-24 hr)	11.060	11.841	93.9	0.93	(0.88 - 0.98)*
C avg (0-12 hr)	11.242	11.951	94.9	0.94	(0.88 - 1.00)*
C avg (12-24 hr)	10.876	11.733	93.0	0.92	(0.87 - 0.97)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
Measurement unit: AUC in ug.hr/mL; C max in ug/mL; C min in ug/mL; C avg in ug/mL

Table 5.1.1 Bioequivalence Analysis Summary I: CBZ
-- ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	221.771	235.758	94.3	0.93	(0.89 - 0.98)*
AUC (0-12 hr)	113.258	119.679	95.4	0.94	(0.89 - 1.00)*
AUC (12-24 hr)	108.533	116.088	93.4	0.92	(0.87 - 0.98)*
C max (0-24 hr)	11.238	11.744	96.9	0.96	(0.91 - 1.01)*
C max (0-12 hr)	10.950	11.523	96.0	0.95	(0.89 - 1.01)*
C max (12-24 hr)	10.350	11.014	94.7	0.93	(0.88 - 0.99)*
C min (0-24 hr)	7.500	8.279	90.3	0.89	(0.83 - 0.95)*
C min (0-12 hr)	7.961	8.769	92.1	0.90	(0.83 - 0.98)*
C min (12-24 hr)	7.759	8.563	90.3	0.89	(0.83 - 0.95)*
C avg (0-24 hr)	9.241	9.824	94.3	0.93	(0.89 - 0.98)*
C avg (0-12 hr)	9.438	9.974	95.4	0.94	(0.89 - 1.00)*
C avg (12-24 hr)	9.046	9.675	93.4	0.92	(0.87 - 0.98)*
FI (0-24 hr)	0.428	0.353	129.7	1.20	(1.07 - 1.35)
FI (0-12 hr)	0.326	0.283	121.2	1.15	(1.02 - 1.29)
FI (12-24 hr)	0.297	0.253	139.5	1.18	(0.96 - 1.45)

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale

Table 5.1.2 Bioequivalence Analysis Summary II: CBZ-epoxide
-- ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	43.625	48.417	91.5	0.89	(0.82 - 0.97)*
AUC (0-12 hr)	21.658	23.721	92.2	0.89	(0.82 - 0.98)*
AUC (12-24 hr)	21.988	24.692	91.3	0.89	(0.82 - 0.97)*
C max (0-24 hr)	2.236	2.540	90.8	0.88	(0.80 - 0.96)*
C max (0-12 hr)	2.105	2.353	91.2	0.88	(0.79 - 0.97)
C max (12-24 hr)	2.116	2.410	91.0	0.88	(0.80 - 0.97)*
C min (0-24 hr)	1.374	1.559	92.2	0.87	(0.77 - 0.98)
C min (0-12 hr)	1.477	1.605	95.1	0.90	(0.80 - 1.01)*
C min (12-24 hr)	1.499	1.766	89.0	0.85	(0.77 - 0.95)
C avg (0-24 hr)	1.818	2.018	91.5	0.89	(0.82 - 0.97)*
C avg (0-12 hr)	1.805	1.978	92.1	0.89	(0.81 - 0.98)*
C avg (12-24 hr)	1.833	2.058	91.4	0.89	(0.82 - 0.97)*
FI (0-24 hr)	0.473	0.488	122.9	1.05	(0.86 - 1.28)
FI (0-12 hr)	0.344	0.370	111.1	1.00	(0.86 - 1.18)*
FI (12-24 hr)	0.338	0.329	125.4	1.07	(0.87 - 1.32)
AUC epoxide-to-CBZ ratio (0-24 hr)	0.205	0.211	96.7	0.96	(0.91 - 1.01)*
AUC epoxide-to-CBZ ratio (0-12 hr)	0.198	0.205	95.9	0.95	(0.90 - 1.00)*
AUC epoxide-to-CBZ ratio (12-24 hr)	0.213	0.218	98.0	0.97	(0.91 - 1.03)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale

Attachment 2

Table 1 - CBZ

Parameters	800 MG (N=9)		1200 MG (N=9)		1600 MG (N=6)	
	SR bid	IR qid	SR bid	IR qid	SR bid	IR qid
AUC0-12	109.3	111.5	115.9	131.4	113.7	114.4
90% C.I.	0.89-1.07		0.79-1.04		0.85-1.12	
AUC12-24	106.98	106.93	111.07	124.04	107.07	117.88
90% C.I.	0.91-1.07		0.85-0.99		0.72-1.07	
AUC0-24	216.24	218.39	227.97	255.46	220.77	232.27
90% C.I.	0.92-1.05		0.82-1.01		0.79-1.08	
CMAX0-12	10.31	10.57	11.50	12.63	11.09	11.29
90% C.I.	0.87-1.08		0.81-1.06		0.83-1.13	
CMAX12-24	10.11	10.18	10.44	11.76	10.58	11.14
90% C.I.	0.92-1.11		0.86-0.96		0.71-1.17	
CMAX0-24	10.71	10.91	11.68	12.63	11.37	11.66
90%C.I.	0.92-1.08		0.84-1.04		0.83-1.13	
CMIN0-12	8.06	8.32	8.02	9.64	7.72	8.14
90%C.I.	0.86-1.09		0.72-1.01		0.75-1.14	
CMIN12-24	7.87	8.09	7.88	8.95	7.42	8.7
90% C.I.	0.86-1.03		0.84-1.01		0.65-1.0	
CMIN0-24	7.66	7.95	7.60	8.83	7.11	7.95
90% C.I.	0.83-1.02		0.79-1.02		0.69-1.04	

Table 2 - CBZE

Parameters	800 MG (N=9)		1200 MG (N=9)		1600 MG (N=6)	
	SR bid	IR qid	SR bid	IR qid	SR bid	IR qid
AUC0-12	15.74	17.86	20.29	24.43	32.58	31.45
90% C.I.	0.75-1.06		0.72-1.02		0.86-1.24	
AUC12-24	16.63	18.61	20.54	24.96	32.18	33.42
90% C.I.	0.81-1.03		0.75-1.0		0.74-1.23	
AUC0-24	32.37	36.47	40.81	49.4	64.73	64.87
90% C.I.	0.79-1.04		0.74-1.03		0.81-1.22	
CMAX0-12	1.50	1.83	2.0	2.36	3.16	3.12
90% C.I.	0.69-1.05		0.73-1.02		0.85-1.23	
CMAX12-24	1.6	1.98	2.0	2.32	3.08	3.2
90% C.I.	0.72-1.08		0.78-1.01		0.72-1.08	
CMAX0-24	1.62	2.1	2.15	2.41	3.3	3.4
90% C.I.	0.69-1.04		0.79-1.04		0.77-1.22	
CMIN0-12	1.11	1.27	1.41	1.75	2.13	1.88
90%C.I.	0.74-1.06		0.71-0.98		0.76-1.68	
CMIN12-24	1.18	1.31	1.35	1.8	2.2	2.4
90% C.I.	0.78-1.03		0.66-1.0		0.69-1.22	
CMIN0-24	1.06	1.23	1.30	1.71	1.95	1.82
90% C.I.	0.72-1.01		0.65-0.97		0.74-1.61	

Table 1.1 Bioequivalence Analysis of CBZ plus CBZE < Total > : 800 mg (N=9)

A parametric approach of ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	248.622	254.878	97.6	0.97	(0.90 - 1.05)*
AUC (0-12 hr)	125.022	129.322	97.1	0.96	(0.87 - 1.07)*
AUC (12-24 hr)	123.600	125.567	98.2	0.98	(0.91 - 1.05)*
C max (0-24 hr)	12.281	12.788	97.9	0.99	(0.90 - 1.08)*
C max (0-12 hr)	11.806	12.263	96.9	0.96	(0.85 - 1.08)*
C max (12-24 hr)	11.670	12.081	98.3	0.99	(0.90 - 1.09)*
C min (0-24 hr)	8.749	9.253	94.2	0.91	(0.82 - 1.01)*
C min (0-12 hr)	9.199	9.614	97.0	0.96	(0.85 - 1.09)*
C min (12-24 hr)	9.101	9.451	95.8	0.93	(0.86 - 1.02)*
C avg (0-24 hr)	10.361	10.619	97.6	0.97	(0.90 - 1.05)*
C avg (0-12 hr)	10.419	10.778	97.1	0.96	(0.87 - 1.07)*
C avg (12-24 hr)	10.299	10.464	98.2	0.98	(0.91 - 1.05)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
Measurement unit: AUC in ug.hr/mL; C max in ug/mL; C min in ug/mL; C avg in ug/mL

Table 1.2 Bioequivalence Analysis of CBZ plus CBZR < Total > : 1200 mg (N=9)

A parametric approach of ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	268.778	304.844	89.5	0.90	(0.81 - 1.01)*
AUC (0-12 hr)	137.200	155.856	89.7	0.90	(0.78 - 1.03)
AUC (12-24 hr)	131.578	149.000	89.4	0.91	(0.84 - 0.99)*
C max (0-24 hr)	13.661	14.992	92.5	0.93	(0.83 - 1.03)*
C max (0-12 hr)	13.457	14.979	91.5	0.91	(0.79 - 1.05)
C max (12-24 hr)	12.360	14.032	89.2	0.91	(0.85 - 0.96)*
C min (0-24 hr)	8.967	10.631	86.3	0.88	(0.77 - 1.01)
C min (0-12 hr)	9.498	11.436	84.6	0.85	(0.72 - 1.01)
C min (12-24 hr)	9.282	10.807	87.8	0.90	(0.81 - 1.01)*
C avg (0-24 hr)	11.200	12.703	89.5	0.90	(0.81 - 1.01)*
C avg (0-12 hr)	11.433	12.990	89.7	0.90	(0.78 - 1.03)
C avg (12-24 hr)	10.968	12.418	89.4	0.91	(0.84 - 0.99)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
Measurement unit: AUC in ug.hr/mL; C max in ug/mL; C min in ug/mL; C avg in ug/mL

Table 1.3 Bioequivalence Analysis of CBZ plus CBZE < Total > : 1600 mg (N=6)

A parametric approach of ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	285.500	297.133	94.8	0.94	(0.79 - 1.11)
AUC (0-12 hr)	146.267	145.833	99.7	0.99	(0.85 - 1.14)*
AUC (12-24 hr)	139.233	151.300	90.4	0.89	(0.72 - 1.10)
C max (0-24 hr)	14.453	14.977	96.9	0.95	(0.82 - 1.11)*
C max (0-12 hr)	14.143	14.342	99.0	0.97	(0.83 - 1.14)*
C max (12-24 hr)	13.598	14.335	94.3	0.92	(0.71 - 1.19)
C min (0-24 hr)	9.228	9.923	90.8	0.89	(0.72 - 1.09)
C min (0-12 hr)	10.018	10.182	98.1	0.96	(0.76 - 1.21)
C min (12-24 hr)	9.678	11.277	84.0	0.82	(0.66 - 1.02)
C avg (0-24 hr)	11.897	12.382	94.8	0.94	(0.79 - 1.11)
C avg (0-12 hr)	12.190	12.153	99.7	0.99	(0.85 - 1.14)*
C avg (12-24 hr)	11.603	12.610	90.3	0.89	(0.72 - 1.10)

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
Measurement unit: AUC in ug hr/mL; C max in ug/mL; C min in ug/mL; C avg in ug/mL

Table 2.1 Bioequivalence Analysis of CBZ plus CBZE < Unbound > : 800 mg (N=3)

A parametric approach of ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	70.278	72.878	96.7	0.96	(0.89 - 1.04)*
AUC (0-12 hr)	35.222	36.822	96.2	0.95	(0.85 - 1.07)*
AUC (12-24 hr)	35.067	36.089	97.2	0.97	(0.90 - 1.04)*
C max (0-24 hr)	3.464	3.698	96.0	0.97	(0.88 - 1.07)*
C max (0-12 hr)	3.328	3.522	95.5	0.95	(0.83 - 1.08)*
C max (12-24 hr)	3.308	3.502	96.8	0.97	(0.88 - 1.08)*
C min (0-24 hr)	2.656	2.632	93.1	0.90	(0.81 - 1.00)*
C min (0-12 hr)	2.581	2.728	96.0	0.95	(0.83 - 1.08)*
C min (12-24 hr)	2.579	2.702	95.3	0.93	(0.85 - 1.01)*
C avg (0-24 hr)	2.929	3.037	96.7	0.96	(0.89 - 1.04)*
C avg (0-12 hr)	2.937	3.069	96.3	0.96	(0.85 - 1.07)*
C avg (12-24 hr)	2.922	3.008	97.2	0.97	(0.90 - 1.04)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
Measurement unit: AUC in ug.hr/mL; C max in ug/mL; C min in ug/mL; C avg in ug/mL

Table 2.2 Bioequivalence Analysis of CBZ plus CBZE < Unbound > : 1200 mg (N=9)

A parametric approach of ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	77.433	88.622	88.9	0.90	(0.80 - 1.01)*
AUC (0-12 hr)	39.367	45.089	89.1	0.89	(0.77 - 1.03)
AUC (12-24 hr)	38.044	43.500	88.8	0.91	(0.83 - 0.99)*
C max (0-24 hr)	3.920	4.344	91.7	0.92	(0.82 - 1.03)*
C max (0-12 hr)	3.857	4.338	90.7	0.91	(0.79 - 1.04)
C max (12-24 hr)	3.570	4.088	88.8	0.90	(0.84 - 0.96)*
C min (0-24 hr)	2.581	3.111	85.3	0.87	(0.76 - 1.00)
C min (0-12 hr)	2.738	3.306	84.5	0.85	(0.72 - 1.00)
C min (12-24 hr)	2.670	3.164	86.7	0.89	(0.79 - 1.00)
C avg (0-24 hr)	3.226	3.696	88.8	0.90	(0.80 - 1.01)*
C avg (0-12 hr)	3.280	3.759	89.0	0.89	(0.77 - 1.03)
C avg (12-24 hr)	3.172	3.624	88.9	0.91	(0.83 - 0.99)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale

Measurement unit: AUC in ug.hr/mL; C max in ug/mL; C min in ug/mL; C avg in ug/mL

Table 2.3 Bioequivalence Analysis of CBZ plus CBZE < Unbound > : 1600 mg (N=6)

A parametric approach of ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	87.600	90.550	95.8	0.94	(0.80 - 1.12)*
AUC (0-12 hr)	44.750	44.333	100.5	0.99	(0.85 - 1.15)*
AUC (12-24 hr)	42.850	46.200	91.5	0.90	(0.72 - 1.11)
C max (0-24 hr)	4.407	4.597	96.3	0.95	(0.81 - 1.10)*
C max (0-12 hr)	4.310	4.353	99.8	0.98	(0.84 - 1.15)*
C max (12-24 hr)	4.157	4.352	94.4	0.92	(0.71 - 1.19)
C min (0-24 hr)	2.815	2.938	94.3	0.92	(0.74 - 1.14)
C min (0-12 hr)	3.045	3.025	100.6	0.98	(0.77 - 1.25)
C min (12-24 hr)	2.982	3.452	85.3	0.83	(0.66 - 1.05)
C avg (0-24 hr)	3.650	3.773	95.8	0.94	(0.79 - 1.12)
C avg (0-12 hr)	3.730	3.695	100.6	0.99	(0.85 - 1.15)*
C avg (12-24 hr)	3.572	3.852	91.5	0.90	(0.72 - 1.11)

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
Measurement unit: AUC in ug.hr/mL; C max in ug/mL; C min in ug/mL; C avg in ug/mL

Attachment 3

Table 4.17.1 ANOVA of 2-Way Crossover Design for CBZ-epoxide T max: all patients

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Source of Variance	SS	df	MS	F value	P value
T max (0-24 hr)	14.292	12.792	Sequence: group 1 vs. group 2	12.00	1	12.000	0.125	0.727
			Error (subject-within-sequence)	2105.67	22	95.712		
			Period: phase I vs. phase II	52.08	1	52.083	1.586	0.221
			Treatment: CBZ-SR vs. Tegretol	27.00	1	27.000	0.822	0.374
			Error (model)	722.67	22	32.849		
T max (0-12 hr)	6.500	5.792	Sequence: group 1 vs. group 2	0.75	1	0.750	0.097	0.758
			Error (subject-within-sequence)	169.48	22	7.704		
			Period: phase I vs. phase II	16.33	1	16.333	2.463	0.131
			Treatment: CBZ-SR vs. Tegretol	6.02	1	6.021	0.908	0.351
			Error (model)	145.90	22	6.632		
T max (12-24 hr)	20.333	19.583	Sequence: group 1 vs. group 2	12.00	1	12.000	1.000	0.328
			Error (subject-within-sequence)	263.92	22	11.996		
			Period: phase I vs. phase II	21.33	1	21.333	2.420	0.134
			Treatment: CBZ-SR vs. Tegretol	6.75	1	6.750	0.766	0.391
			Error (model)	193.92	22	8.814		

* : $p < 0.05$; ** : $p < 0.01$; *** : $p < 0.001$

group 1 = CBZ-SR (Phase I) & Tegretol (Phase II); group 2 = Tegretol (Phase I) & CBZ-SR (Phase II)

Table 4.17.2 ANOVA of 2-Way Crossover Design for CBZ-epoxide T max: 800 mg

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Source of Variance	SS	df	MS	F value	P value
T max (0-24 hr)	14.292	12.792	Sequence: group 1 vs. group 2	12.00	1	12.000	0.125	0.727
			Error (subject-within-sequence)	2105.67	22	95.712		
			Period: phase I vs. phase II	52.08	1	52.083	1.586	0.221
			Treatment: CBZ-SR vs. Tegretol	27.00	1	27.000	0.822	0.374
			Error (model)	722.67	22	32.849		
T max (0-12 hr)	6.500	5.792	Sequence: group 1 vs. group 2	0.75	1	0.750	0.097	0.758
			Error (subject-within-sequence)	169.48	22	7.704		
			Period: phase I vs. phase II	16.33	1	16.333	2.463	0.131
			Treatment: CBZ-SR vs. Tegretol	6.02	1	6.021	0.908	0.351
			Error (model)	145.90	22	6.632		
T max (12-24 hr)	20.333	19.583	Sequence: group 1 vs. group 2	12.00	1	12.000	1.000	0.328
			Error (subject-within-sequence)	263.92	22	11.996		
			Period: phase I vs. phase II	21.33	1	21.333	2.420	0.134
			Treatment: CBZ-SR vs. Tegretol	6.75	1	6.750	0.766	0.391
			Error (model)	193.92	22	8.814		

* : $p < 0.05$; ** : $p < 0.01$; *** : $p < 0.001$

group 1 = CBZ-SR (Phase I) & Tegretol (Phase II); group 2 = Tegretol (Phase I) & CBZ-SR (Phase II)

Table 4.17.3 ANOVA of 2-Way Crossover Design for CBZ-epoxide T max: 1200 mg

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Source of Variance	SS	df	MS	F value	P value
T max (0-24 hr)	14.292	12.792	Sequence: group 1 vs. group 2	12.00	1	12.000	0.125	0.727
			Error (subject-within-sequence)	2105.67	22	95.712		
			Period: phase I vs. phase II	52.08	1	52.083	1.586	0.221
			Treatment: CBZ-SR vs. Tegretol	27.00	1	27.000	0.822	0.374
			Error (model)	722.67	22	32.849		
T max (0-12 hr)	6.500	5.792	Sequence: group 1 vs. group 2	0.75	1	0.750	0.097	0.758
			Error (subject-within-sequence)	169.48	22	7.704		
			Period: phase I vs. phase II	16.33	1	16.333	2.463	0.131
			Treatment: CBZ-SR vs. Tegretol	6.02	1	6.021	0.908	0.351
			Error (model)	145.90	22	6.632		
T max (12-24 hr)	20.333	19.583	Sequence: group 1 vs. group 2	12.00	1	12.000	1.000	0.328
			Error (subject-within-sequence)	263.92	22	11.996		
			Period: phase I vs. phase II	21.33	1	21.333	2.420	0.134
			Treatment: CBZ-SR vs. Tegretol	6.75	1	6.750	0.766	0.391
			Error (model)	193.92	22	8.814		

* : p < 0.05; ** : p < 0.01; *** : p < 0.001

group 1 = CBZ-SR (Phase I) & Tegretol (Phase II)

group 2 = Tegretol (Phase I) & CBZ-SR (Phase II)

Table 4.17.4 ANOVA of 2-Way Crossover Design for CBZ-epoxide T max: 1600 mg

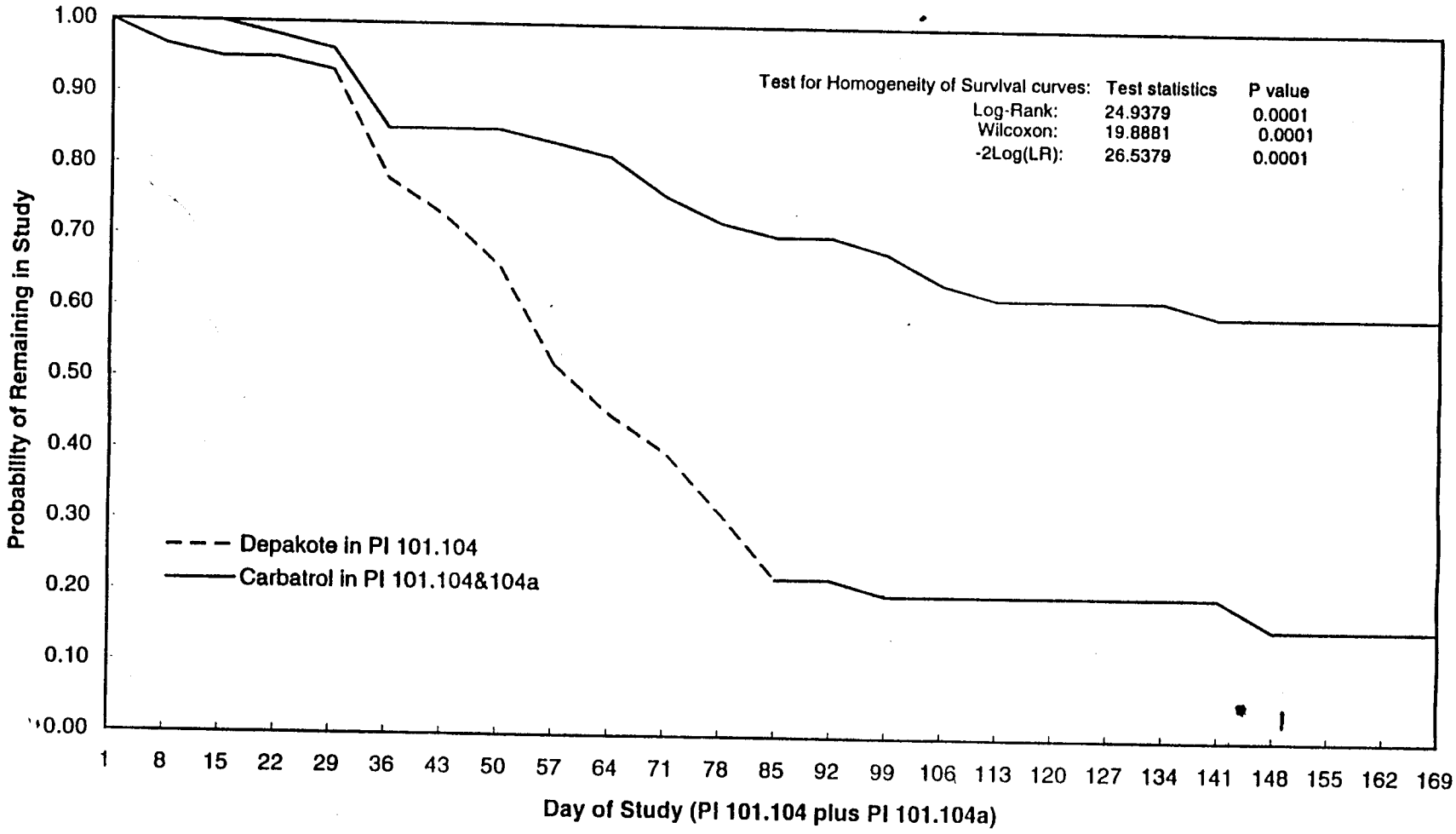
PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Source of Variance	SS	df	MS	F value	P value
T max (0-24 hr)	14.292	12.792	Sequence: group 1 vs. group 2	12.00	1	12.000	0.125	0.727
			Error (subject-within-sequence)	2105.67	22	95.712		
			Period: phase I vs. phase II	52.08	1	52.083	1.586	0.221
			Treatment: CBZ-SR vs. Tegretol	27.00	1	27.000	0.822	0.374
			Error (model)	722.67	22	32.849		
T max (0-12 hr)	6.500	5.792	Sequence: group 1 vs. group 2	0.75	1	0.750	0.097	0.758
			Error (subject-within-sequence)	169.48	22	7.704		
			Period: phase I vs. phase II	16.33	1	16.333	2.463	0.131
			Treatment: CBZ-SR vs. Tegretol	6.02	1	6.021	0.908	0.351
			Error (model)	145.90	22	6.632		
T max (12-24 hr)	20.333	19.583	Sequence: group 1 vs. group 2	12.00	1	12.000	1.000	0.328
			Error (subject-within-sequence)	263.92	22	11.996		
			Period: phase I vs. phase II	21.33	1	21.333	2.420	0.134
			Treatment: CBZ-SR vs. Tegretol	6.75	1	6.750	0.766	0.391
			Error (model)	193.92	22	8.814		

group 1 = CBZ-SR (Phase I) & Tegretol (Phase II); group 2 = Tegretol (Phase I) & CBZ-SR (Phase II)

* : $p < 0.05$; ** : $p < 0.01$; *** : $p < 0.001$

Attachment 4
Survival analysis

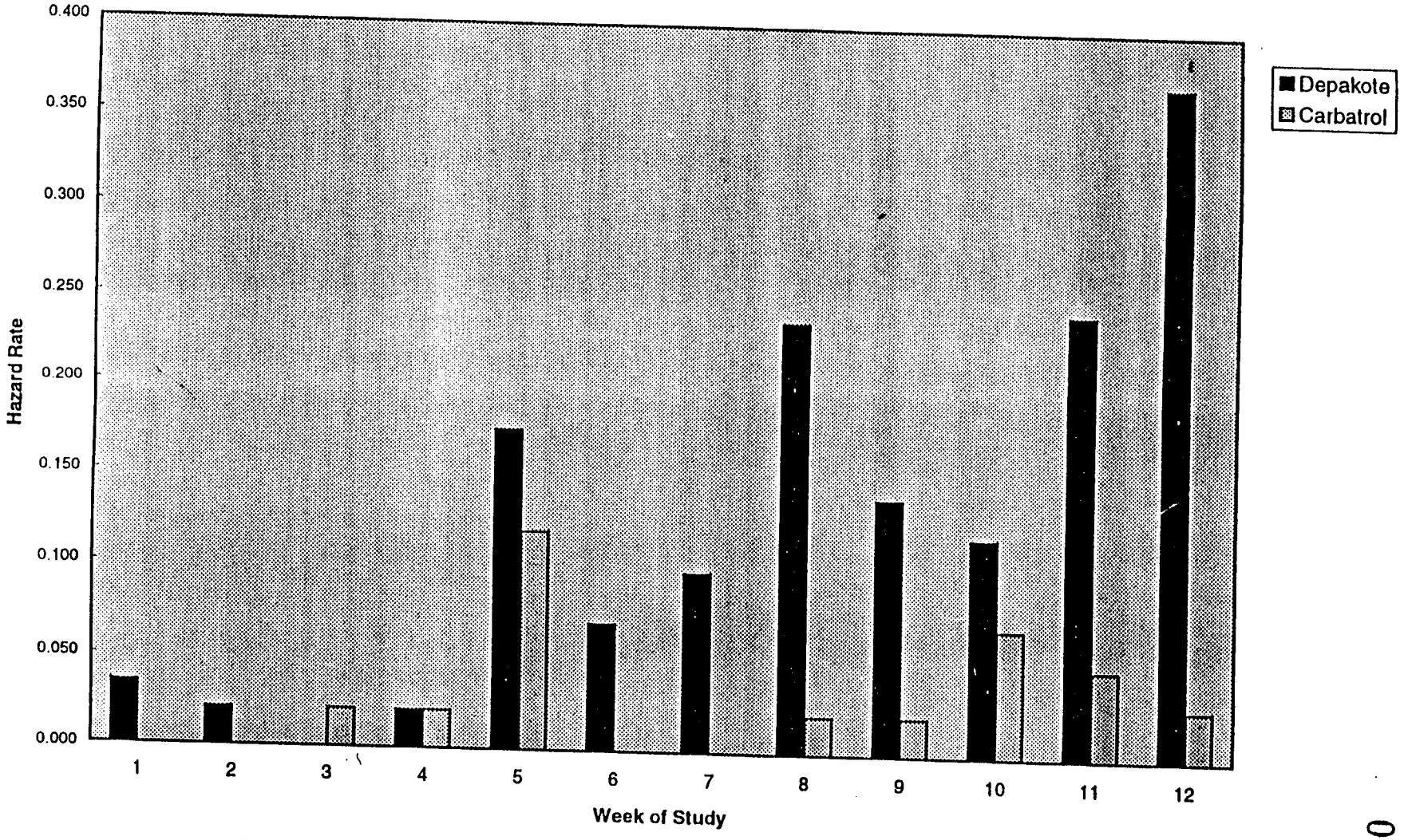
Figure 1.1a Survival Function of All Patients for the 24-Week Period of PI_101.104 & PI_101.104A (N=121)



8 1291

0106

Figure 1.2 Weekly Hazard Rate Estimates for the 12-Week Study Period



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20712

CHEMISTRY REVIEW(S)

CHEMISTRY

NDA 20-712 Carbatrol® (carbamazepine) Controlled Release Capsules
Classification: 3S

Date	Document	Reviewer	Tab
09-23-97	Chemistry Review #4 (with supervisory sign-off by Dr. Guzewska)	Martha Heimann, Ph.D.	J
07-15-97	Chemistry Review #3 (with supervisory sign-off by Dr. Blum)	Martha Heimann, Ph.D.	J
03-04-97	Team Leader Memo	Stanley Blum, Ph.D.	J
03-04-97	CHEMISTRY NDA Review #2 (Review of firm's response to deficiencies)		K
01-10-97	CHEMISTRY NDA Review #1	Martha Heimann, Ph.D.	K
10-11-96	Reviews of DMF:		K

LABELING AND NOMENCLATURE REVIEW L

ESTABLISHMENT INSPECTIONS M

11-25-96 EER Form (- unacceptable; others are acceptable)
01-23-97 District Office Letter to Firm (- acceptable)
02-07-97 FUR Form from Division's Chemist
06-25-97 EIR - ACCEPTABLE

ENVIRONMENTAL ASSESSMENT Mc

07-06-96	EA Review with Deficiencies	Martha Heimann, Ph.D.
07-19-96	EA Deficiencies sent to firm	
10-02-96	Firm's response to EA deficiencies (cover letter in Document History volume)	
12-12-96	REVIEW/FONSI	Martha Heimann, Ph.D.
01-13-97	Memo from Nancy Sager	
01-27-97	Emails between Martha Heimann & Nancy Sager	
02-01-97	**COMPLETED EA & FONSI**	Mc

CHEMISTRY DEFICIENCY LETTER #2 (faxed/mailed to firm on 8/1/97) N
CHEMISTRY DEFICIENCY LETTER #1 (faxed/mailed to firm on 2/4/97) N

XXXX indicates documents which are new to the action package since AE action occurred.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-712

CHEMISTRY REVIEW: # 4 **DATE REVIEWED:** 22-SEP-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N(BC)	13-AUG-97	13-AUG-97	14-AUG-97
N(BC)	02-SEP-97	02-SEP-97	02-SEP-97

NAME AND ADDRESS OF APPLICANT: Shire Laboratories, Inc (formerly Pharmavene, Inc.)
1550 East Gude Drive
Rockville, MD 20850

DRUG PRODUCT NAME:

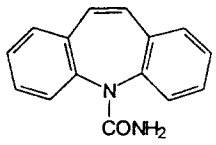
Proprietary:	CARBATROL®
Nonproprietary/Established/USAN:	carbamazepine
Code Name/#:	PI 101
Chem. Type/Ther. Class:	3 S

DESI / PATENT STATUS: N/A

PHARMACOLOGICAL CATEGORY/ INDICATION:	Anti-convulsant
DOSAGE FORM:	Extended-release capsule
STRENGTHS:	200 mg, 300 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	XX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

5*H*-dibenz[b,f]azepine-5-carboxamide
CAS Registry Number: 298-46-4
Molecular Formula: $C_{15}H_{12}N_2O$ Molecular Weight: 236.27



SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS: NDA 16-606 (Tegretol),

CONSULTS: EA review was completed and sent, to Ms. Sager, HFD-357. FONSI signed 01-FEB-97.

REMARKS / COMMENTS:

The 13-AUG-97 and 02-SEP-97 amendments satisfactorily addressed the remaining CMC review concerns for Carbatrol and are in response to deficiencies contained in the 01-AUG-97 information request letter. The most critical issue is the specification limits for the The firm has accepted a limit of NMT . The 02-SEP-97 submission provides analytical data, and regression analyses, for levels in reserve stability samples, to support a 24 month expiry Methods Validation is currently in progress.

CONCLUSIONS AND RECOMMENDATIONS:

Recommend Approval for Chemistry. The action letter should include the standard reminder about cooperation with Methods Validation and the following comment should be forwarded to the firm:

The tentative expiration dating period for Carbatrol capsules is 24 months, calculated from date of initial pellet manufacture.

cc: Orig. NDA 20-712
HFD-120/Division File
HFD-120/MHeimann/22-SEP-97
HFD-120/JWare
HFD-120/MGuzewska/Init.: MG 9.23.97

Martha R. Heimann 9/22/97
Martha R. Heimann, Ph.D., Review Chemist
Filename: **N20-712.004**

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS JUL 15 1997
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-712

CHEMISTRY REVIEW: # 3 **DATE REVIEWED:** 07-JUL-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N(BC) (response to AE letter)	19-MAY-97	20-MAY-97	20-MAY-97
N(BC) (withdraw Metuchen Analytical)	18-JUN-97	19-JUN-97	19-JUN-97
N(BC) (revised Methods Validation package)	23-JUN-97	24-JUN-97	19-JUN-97

NAME AND ADDRESS OF APPLICANT: Shire Laboratories, Inc (formerly Pharmavene, Inc.)
1550 East Gude Drive
Rockville, MD 20850

DRUG PRODUCT NAME:

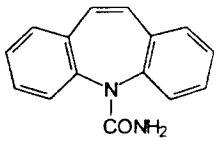
Proprietary:	CARBATROL®
Nonproprietary/Established/USAN:	carbamazepine
Code Name/#:	PI 101
Chem. Type/Ther. Class:	3 S

DESI / PATENT STATUS: N/A

PHARMACOLOGICAL CATEGORY/ INDICATION:	Anti-convulsant
DOSAGE FORM:	Extended-release capsule
STRENGTHS:	200 mg, 300 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	XX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

5*H*-dibenz[b,f]azepine-5-carboxamide
CAS Registry Number: 298-46-4
Molecular Formula: $C_{15}H_{12}N_2O$ Molecular Weight: 236.27



SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS: NDA 16-606 (Tegretol),

CONSULTS: EA review was completed and sent, to Ms. Sager, HFD-357. FONSI signed 01-FEB-97.

REMARKS / COMMENTS:

The 19-MAY-97 amendment is a response to deficiencies contained in the 20-MAR-97 approvable letter. Most of the issues raised have been resolved but the firm has not agreed to specification limits for the . The information submitted indicates that formation is a more serious problem than the firm's 13-FEB-97 amendment indicated and will limit product shelf life The firm has withdrawn one testing laboratory, from the NDA due to compliance problems. Compliance has issued an acceptable EIR for the application and Methods Validation has been initiated.

CONCLUSIONS AND RECOMMENDATIONS:

NDA is Approvable for Chemistry provided the sponsor accepts the recommended impurity specifications and agrees to limit initial expiry to 18 months. All product labeling must be revised by replacement of the phrase "carbamazepine extended-release beads in capsules" with the correct established name "carbamazepine extended-release capsules".

cc: Orig. NDA 20-712
HFD-120/Division File
HFD-120/MHeimann/07-JUL-97
HFD-120/JWare
HFD-120/SBlum/Init.:

7/15/97

Martha R. Heimann 7/7/97
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-712.003

DIVISION OF NEUROPHARMACOLOGICALDRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-712

CHEMISTRY REVIEW: # 2 **DATE REVIEWED: 25-FEB-97**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	03-APR-96	03-APR-96	12-APR-96
Amendment	26-DEC-96	27-DEC-96	N/A
Amendment	13-FEB-97	14-FEB-97	14-FEB-97

NAME AND ADDRESS OF APPLICANT: Pharmavene, Inc.
1550 East Gude Drive
Rockville, MD 20850

DRUG PRODUCT NAME:

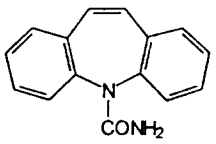
Proprietary:	CARBATROL®
Nonproprietary/Established/USAN:	carbamazepine
Code Name/#:	PI 101
Chem. Type/Ther. Class:	3 S

DESI / PATENT STATUS: N/A

PHARMACOLOGICAL CATEGORY/ INDICATION: Anti-convulsant
DOSAGE FORM: Extended-release capsule
STRENGTHS: 200 mg, 300 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

5*H*-dibenz[b,f]azepine-5-carboxamide
CAS Registry Number: 298-46-4
Molecular Formula: $C_{15}H_{12}N_2O$ Molecular Weight: 236.27



SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS: NDA 16-606 (Tegretol),

CONSULTS: EA review was completed and sent, to Ms. Sager, HFD-357. FONSI signed 01-FEB-97.

REMARKS/ COMMENTS:

The 13-FEB-97 amendment is a response to information request letter sent to the firm on 4-FEB-97. Several deficiencies have not been satisfactorily addressed by the sponsor. Methods Validation has not been initiated. The sponsor submitted a new method (with little or no supporting data) in the 13-FEB-97 amendment. Compliance issued a Withhold Approval recommendation on 25-NOV-96 based on deficiencies at the
According to information supplied by the firm, the NJ District Office reinspected the site in January 1997 and found it acceptable. This has not been verified by Compliance, a follow-up EER was sent on 7-FEB-97

CONCLUSIONS AND RECOMMENDATIONS:

NDA is NOT Approvable for Chemistry at this time.

cc: Orig. NDA 20-712
HFD-120/Division File
HFD-120/MHeimann/25-FEB-97
HFD-120/JWare
HFD-120/SBlum/Init.: 3/4/97

Martha R. Heimann 2/25/97
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-712.002

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-712

CHEMISTRY REVIEW: # 1

DATE REVIEWED: 23-SEP-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	03-APR-96	03-APR-96	• 12-APR-96

NAME AND ADDRESS OF APPLICANT: Pharmavene, Inc.
1550 East Gude Drive
Rockville, MD 20850

DRUG PRODUCT NAME:

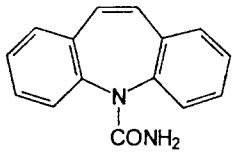
Proprietary:	CARBATROL™
Nonproprietary/Established/USAN:	carbamazepine
Code Name/#:	PI 101
Chem. Type/Ther. Class:	3 S

DESI / PATENT STATUS: N/A

PHARMACOLOGICAL CATEGORY/ INDICATION:	Anti-convulsant
DOSAGE FORM:	Extended-release capsule
STRENGTHS:	200 mg, 300 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	XX Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA AND MOLECULAR FORMULA:

5*H*-dibenz[b,f]azepine-5-carboxamide
CAS Registry Number: 298-46-4
Molecular Formula: $C_{15}H_{12}N_2O$ Molecular Weight: 236.27



SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS: NDA 16-606 (Tegretol)

CONSULTS: N/A

REMARKS / COMMENTS:

The drug product is a capsule containing a mixture of immediate release, extended-release and enteric coated pellets. The manufacturing process was changed several times during product development and does not appear to be well controlled. There are several deficiencies in the regulatory specifications and methods for the drug product. Inspections have not been performed.

CONCLUSIONS AND RECOMMENDATIONS: NDA is NOT Approvable for Chemistry at this time.

cc: Orig. NDA 20-712
HFD-120/Division File
HFD-120/MHeimann/23-SEP-96
HFD-120/JWare
HFD-120/SBlum/Init.: AWB 1/16/97

Martha R Heimann 9/23/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: N20-712.R01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20712

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

CARBATROL® CAPSULES

(carbamazepine extended-release capsules)

200 and 300 mg

NDA 20-712

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Neuropharmacological Drug Products

HFD-120

Finding of No Significant Impact
NDA 20-712
Carbamazepine Extended-Release Capsules

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decision maker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application (NDA 20-712) for Carbatrol® Capsules, Pharmavene, Inc. has prepared an environmental assessment (21 CFR 25.31a(a)) which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product.

Carbamazepine is a synthetic drug which is commonly prescribed for treatment of epilepsy and trigeminal neuralgia. The extended release formulation is intended for use as 200 mg and 300 mg capsules to be taken orally twice daily while the immediate release formulations are typically administered four times daily.

The drug substance will be manufactured by a contract manufacturer at a foreign facility. The drug product will be manufactured within the United States at contract facilities. The finished drug product will be dispensed by prescription only. Patient use and disposal will be in both residences and hospitals. Unused or expired product will be shipped for incineration at off-site facilities.

During the Carbatrol® capsule manufacturing process, particulate emissions, wastewater discharges and solid waste may result. Particulate emissions (carbamazepine and common drug excipients) are controlled during the manufacturing processes by appropriate particle filters. No volatile organic compounds (VOC's) are used in the manufacturing process. Wastewater, primarily from equipment cleaning, is treated prior to discharge into local sewage systems. Solid process waste is shipped for incineration at an off-site licensed facility. All production, packaging and waste disposal facilities operate in compliance with Federal, state and local regulations.

Based on peak year production estimates for the Carbatrol® capsules, Pharmavene has calculated the Maximum Expected Environmental Concentration (MEEC) for carbamazepine as a result of approval of NDA 20-712. Based on a calculated MEEC of less

than 1 part per billion, CDER has determined that Carbatrol® capsules meet the requirements for a Tier 0 approach and that no additional assessment of environmental fate and effects is required. Pharmavene has, however, cited the Environmental Assessment for a competitive product, Tegretol-XR® (carbamazepine extended-release tablets) for physico-chemical properties and toxicity data to support a conclusion that no significant toxic effects will occur due to use of the product.

Carbamazepine drug substance and Carbatrol® capsules will be manufactured at existing facilities, land use will not be altered. Capsule manufacture and packaging require minimal amounts of energy and raw materials.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Any residues of carbamazepine entering the environment as a result of administering the drug to humans are expected to be much lower than the minimum concentration at which any toxic effect is likely to occur.

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TABLE OF CONTENTS (CONTINUED)

Location of Information in Non-Confidential/Confidential Appendices

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
1. Date	***	X	
2. Name of Applicant/Petitioner	***	X	
3. Address	***	X	
4. Description Proposed Action	a. Requested Approval	X	
	b. Need for Action	*Indications and use	*Formulation rationale
	c. Production Locations	*Names and addresses of facilities released under FOIA procedures	*Names and address of facilities excluded from public release under FOIA procedures
	d. Locations of Use	X	
	e. Disposal Sites	*Disposal method(s) *Statement regarding licensing/permitting of disposal facilities	*Specific information regarding contract disposal companies/facilities, permits
5. Identification of Chemical Substances that are the Subject of the Proposed Action	a. Nomenclature	X	
	b. CAS Number	X	
	c. Molecular Formula	X	
	d. Molecular Weight	X	
	e. Structural Formula	X	
	f. Physical Description	X	
	g. Additives	* General discussion	
	h. Impurities	* General discussion	

TABLE OF CONTENTS (CONTINUED)

Location of Information in Non-Confidential/Confidential Appendices

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
6. Introduction of Substances into the Environment	a. Substances Expected to be Emitted	*General Discussion and reference to confidential appendix	*Specific Information
	b. Controls Exercised	X	
	c. Citation/Statements of Compliance	*Citations *Signed Statements for facilities released under FOIA procedures *General statements and reference to confidential appendix for facilities not released under FOIA procedures	*Signed statements for facilities excluded from release under FOIA procedures
	d. Effect of Approval on Compliance with Current Emission Requirements	X	
	e. Expected Introduction Concentrations	*Summary discussion	*Specific calculations * 5th year production estimates
7. Fate of emitted Substance in the Environment	a. Identification of Chemical Compounds of Interest	*Substances expected to enter or exist in the environment *Summary discussion of toxicity/activity of predominant SRS's relative to the parent (active) compound	
	b. Physical/Chemical Characterization	*Test results	
	c. Depletion Mechanisms	*Test results	
	d. Expected Environmental Concentrations	*Summary discussion	*Specific information that would disclose production volumes
	e. Summary	X	
8. Environmental Effects of Released Substances	***	*Test results and summary discussion	

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Location of Information in Non-Confidential/Confidential Appendices

EA FORMAT ITEM	SUBSECTION	NON-CONFIDENTIAL	CONFIDENTIAL
9. Use of Resources and Energy	a. Natural Resources and Energy	X	
	b. Effect on Endangered or Threatened Species	X	
	c. Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places	X	
10. Mitigation Measures	***	X	
11. Alternatives to the Proposed Action	***	X	
12. List of Preparers	***	X	*CV's for the List of Preparers
13. Certification	***	X	
14. References	***	X	
15. Appendices	***	*Merck Index References *MSDS Sheets *Tegretol-XR EA	
16. Confidential Appendices			*Confidential Appendices 1 through 10

ENVIRONMENTAL ASSESSMENT (CONTINUED)

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1. Date of this Environmental Assessment Amendment: September 16, 1996
   Date of original Environmental Assessment: December 29, 1995

2. Name of Applicant: Pharmavene, Inc.

3. Applicants Address: 1550 East Gude Drive, Rockville, MD 20850

ENVIRONMENTAL ASSESSMENT (CONTINUED)

4. Description of Proposed Action

---

a. Requested Approval

Pharmavene, Inc. of 1550 East Gude Drive, Rockville, Maryland has filed a New Drug Application Number 20-712 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic for, Carbatrol® (Carbamazepine Sustained-Release Capsules) 200 mg and 300 mg capsules, packaged in HDPE bottles. Pharmavene, Inc. is requesting approval to manufacture, package, distribute, and market Carbatrol®, 200 mg and 300 mg Capsules, under a contract basis.

The finished drug product is a sustained-release capsule that contains 200 mg or 300 mg Carbamazepine, USP. Carbamazepine is currently marketed in the United States under the trade name: Tegretol®. Other trade names are Bison; Calepsin; Carbelon; Epital; Finlepsin; Sirtal; Stazepine; Telesmin; and Timonil.

b. Need for Action

Carbamazepine Sustained-Release Capsules are indicated for the treatment of some forms of epilepsy. The current patient population for such an indication is about one percent of the population or 2.0 - 2.5 million people. Carbamazepine Sustained-Release Capsule formulation is designed to provide a twice-a-day (BID) dosing regime. The rationale for the formulation is discussed in detail in the Confidential Appendix 1. (See page 195).

c. Production Locations

Carbamazepine, USP is synthesized by a source identified as Raw Material Site 1. Carbamazepine Sustained-Release Capsules will be manufactured in two stages. The first stage of the process will be conducted at Manufacturing Site 1, and the second stage of the process will be conducted at Manufacturing Site 2. The Quality Control laboratory which will test in-process intermediate pellets and finished product (capsule) is designed as Quality Control Site 1. See the Confidential Appendix 2, page 196, for full details on the location and type of environment for the manufacturing sites. Each of these locations are semi urban areas. No effects upon endangered or threatened species are anticipated and

the facilities are not located on historic sites. Further information regarding production can be found in Section 6 and Section 9 of the Environmental Assessment Statement. (See pages 021 and 043, respectively.)

d. Locations of Use

The product will be available by prescription only in HDPE bottles of 120 capsules in hospitals and pharmacies nationwide for hospital use and long term in-home self administration by the patient.

e. Disposal Sites

The types of environments where the product will be used and disposed of encompass the entire range of environments existing in the United States and Puerto Rico (possibly excepting wilderness): rural, suburban and urban. Sewage treatment plants, landfills, and incinerators exist all across the US and Puerto Rico and their placement is not confined to any one type of environment. Further information on disposal can be found in Section 6, page 021 of this document with regard to disposal sites used by Manufacturing Sites 1 and 2 and Quality Control Site 1. It is impossible to know which of these various disposal facilities will be involved in the treatment and disposal of metabolized and/or unused, prescribed Carbatrol®.

Carbatrol® finished product will be marketed and distributed by:

Athena Neurosciences
800 Gateway Blvd.
South San Francisco, CA

Any unusable returned or expired materials will be transported via common carrier within the United States and where warranted, would be disposed of via incineration by:

Integrated Environmental Services (IES)
499 High Street
Oakland, CA
EPA License No.: CAD 980890321

IES operates in compliance with applicable California standards. Certificates of Destruction would be issued by IES for all materials destroyed.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

5. Identification of Chemical Substances that are the Subject of the Proposed Action

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Carbamazepine Sustained-Release Capsule, a capsule dosage form of carbamazepine, is a multi-pellet composition, consisting of three different types of pellets. The pellets are uncoated, or coated with one of two types of coating, yielding the three types of pellets: the uncoated immediate-release pellets, sustained-release coated pellets, and enteric-release coated pellets. All of the components are either USP/NF, or made from USP/NF materials and are commonly found in Pharmaceutical products presently marketed in the United States for in-home use. Each ingredient in the formulation will be addressed individually in this section.

Please see Section 14, References, page 049 and Section 15, Non-Confidential Appendices, page 050, for further information including Merck Index references, MSDS Sheets or see the current USP monographs for each component.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

5. Identification of Chemical Substances that are the Subject of the Proposed Action

---

a. Nomenclature

i. Established Name (U.S. Adopted Name -USAN)

Carbamazepine, USP is named in the United States Pharmacopoeia (USP).

ii. Brand/Proprietary Name

Trade names for Carbamazepine are: Atretol™ Tablets; Biston; Calepsin; Carbelan; Epitol®; Finlepsin; Sirtal; Stazepine; Tegretal; Tegretol®; Telesmin; and Timonil.

iii. Chemical Names

1. Chemical Abstracts Index Name

2,3:6,7-Dibenzapine-1-carboxylic acid, amide

2. Systematic Chemical Name

5-Carbamoyl-5H-dibenz[b,f]azepine and

5H-Dibenz[b,f]azepine-5-carboxamide

b. Chemical Abstract Service (CAS) Registration Number

The Chemical Abstract Service (CAS) number is [*298-46-4*].

c. Molecular Formula

Carbamazepine is an iminostilbene derivative with the empirical formula $C_{15}H_{12}N_2O$.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

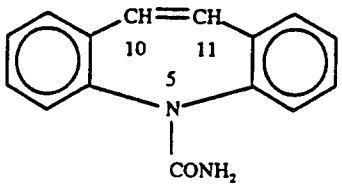
---

d. Molecular Weight

Carbamazepine is a hydrophobic drug and according to USP 23/NF 18, it has a molecular weight of 236.27.

e. Structural (graphic) Formula

The structure of carbamazepine is shown below.



f. Physical Description

Carbamazepine is a white to off-white crystalline powder. It is soluble in alcohol, and practically insoluble in water. The vapor pressure is negligible.

Carbamazepine is synthesized and supplied by Raw Material Site 1. (Section 16, Confidential Appendix 2, see page 196). Carbamazepine, as supplied by Raw Material Site 1, conforms to the specifications of USP 23.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

---

g. Additives

i. Microcrystalline Cellulose, NF

Microcrystalline Cellulose, NF is also known under other names: Carboxymethyl Cellulose sodium; Carboxymethyl Ether Cellulose sodium salt; CMC; Sodium Carboxymethyl Cellulose; Sodium Cellulose Glycolate; Carmethose; Cel-O-Brant; Cethylose; Glykocellon; Carbose D; Thylose; Xylomucine; Tylose MGA; Cellolax; Polycell; Avicel.

Microcrystalline Cellulose is the purified, partially depolymerized cellulose which occurs as a white, odorless, tasteless crystalline powder composed of porous particles. It has a molecular weight of approximately 36,000, with an empirical formula of $(C_6H_{10}O_{15})_{220}$ and a CAS number [*9004-34-6*]. The vapor pressure is negligible.

g. Additives (continued)

ii. Lactose Monohydrate, NF

Lactose Monohydrate, NF is also known as: α-Lactose Monohydrate; 4-O-β-D-Galactopyranosyl-D-Glucose; 4-(β-D-Galactosido)-D-Glucose; milk sugar.

Lactose is a natural disaccharide consisting of galactose and glucose. It exists as two anomeric forms, alpha and beta which are normally handled respectively as the monohydrate and the anhydrous material. Though alpha lactose is available primarily as the monohydrate, two anhydrous forms also exist.

Lactose Monohydrate, NF is the monohydrate of lactose and is obtained as a white crystalline powder which is sweet-tasting and odorless. It has a molecular weight of 360.31, the empirical formula is $C_{12}H_{22}O_{11}H_2O$ and CAS number [*5989-81-1*]. The vapor pressure is negligible.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

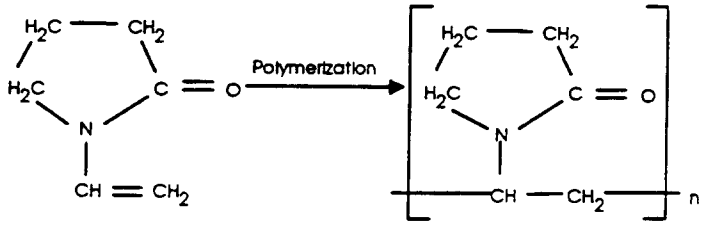
---

g. Additives (continued)

iii. Povidone, USP

Povidone, USP is also known as: 2-Pyrrolidinone; 1-Ethenyl; Homopolymer; 1-Vinyl-2-Pyrrolidinone Polymer.

Povidone is a white to off-white water soluble powder and the polymerization reaction to form the structure of polyvinylpyrrolidone is shown below:



N - Vinylpyrolidone Polyvinylpyrrolidone

The polymer is characterized by its viscosity in aqueous solution relative to that of water. The CAS number is [*9003-39-8*]. The vapor pressure is negligible.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

---

g. Additives (continued)

iv. Sodium Lauryl Sulfate, NF

Sodium Lauryl Sulfate , NF is also known as Sulfuric Acid Monododecyl Ester Sodium Salt; Sodium Monododecyl Sulfate.

Sodium Lauryl Sulfate (SLS) is a white to pale yellow crystalline powder or flake. SLS is freely water soluble. It has a smooth feel, bitter taste and a slight odor of fatty substances. The structural formula of SLS is $CH_3(CH_2)_{10}CH_2SO_4Na$ with a CAS number *[151-21-3]*. The vapor pressure is negligible.

g. Additives (continued)

v. Talc, USP

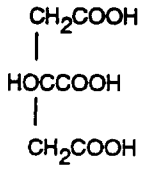
Talc is also known as Talcum, French Chalk, Soapstone, and Steatite, to name a few. Talc is the well known ingredient in Baby Powder.

Talc, USP is a native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate with an empirical formula of $3MgO{\cdot}4SiO_2H_2O$ the CAS number is [*14807-96-6*]. Talc is insoluble in water and has a negligible vapor pressure. It is a very fine, white to grayish white, impalpable, crystalline powder with a slight earthy odor. Talc, USP adheres readily to skin, is soft to touch and is free from grittiness.

g. Additives (continued)

vi. Citric Acid, USP (Anhydrous)

Citric Acid, USP is also known as: 2-hydroxy-1, 2, 3-Propanetricarboxylic Acid. Citric acid is a white crystalline solid, with a molecular weight of 192.12, and melting point of 153 °C, an empirical formula of $C_6H_8O_7$ and a molecular structure of:



The CAS number for Citric Acid is [*77-92-9*]. The vapor pressure is negligible. At 25 °C pK_1 is 3.1; pK_2 is 4.8; pK_3 is 6.4. Citric acid is soluble in water, with a solubility of 59.2 % at 20 °C.

Citric acid is incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, and sulfides. It is commonly used as an acidulent in beverages, confectioneries, pharmaceutical syrups, elixers and tablets to adjust the pH of the formulation.

g. Additives (continued)

vii. Polyethylene Glycol, NF

Polyethylene Glycol, NF is also known as: PEG (Pharmacy equivalent name); α-hydro-ω-hydroxy-Poly(oxy-1, 2-ethanediyl).

Polyethylene Glycol (PEG) is a clear to slightly yellow, viscous liquid with a slight odor. The structural formula of PEG is $HOCH_2(CH_2OCH_2)_nCH_2OH$. The CAS number is [25322-68-3]. The vapor pressure at 20°C is < 0.01 mmHg. PEG is 100% soluble in water.

g. Additives (continued)

viii. Purified Water, USP

Purified Water, USP has a molecular weight of 18.02 and the empirical formula H_2O. The CAS number is [7732-18-5], and a vapor pressure of 18 mmHg.

Purified Water, USP is used to prepare the formulation of the core pellets, the enteric-coating and the sustained-release coating.

The Purified Water, USP to date has been a qualified source of Water, USP at each manufacturing site, or supplied by Baxter as Purified Water, USP Bottled For Injection. The final process will utilize Purified Water, USP as supplied from the validated Niro Inc. water purification system.

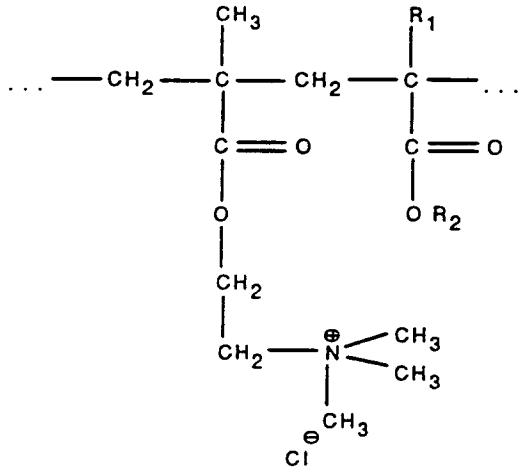
5. Identification of Chemical Substances that are the Subject of the Proposed Action

---

g. Additives (continued)

ix. Eudragit RL30D

Eudragit RL30D is a milky white, slightly viscous aqueous dispersion with a faint characteristic odor and is miscible with water. Eudragit RL30D is an aqueous dispersion of copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The ammonium groups occur as salts and are responsible for the permeability of the film. The monomeric structure is shown below:



$R_1 = H, CH_3$
$R_2 = CH_3, C_2H_5$

The water used for manufacture meets the specifications for Purified Water, USP. Additionally, the dispersion contains 0.25% Sorbic Acid, NF and small amounts of Sodium Hydroxide, NF. It is an aqueous acrylic polymer dispersion containing 30%solids. The active polymer in Eudragit RL30D is the USP material Ammonio Methacrylate Copolymer, Type A, CAS number [33434-24-1]. The mean molecular weight is approximately 150,000. The vapor pressure at 20°C is about 18 mmHg.

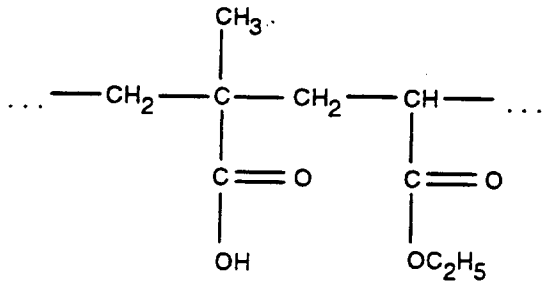
5. Identification of Chemical Substances that are the Subject of the Proposed Action

---

g. Additives (continued)

x. Eudragit L30D-55

Eudragit L30D-55 is a milky white, slightly viscous aqueous dispersion with a slightly sour odor and is miscible with water. Eudragit L30D-55 is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The chemical structure of the monomer is shown below:



The ratio of the free carboxyl grouped to ester groups is approximately 1:1.

The water used for Manufacture meets the specifications for Purified Water, USP. Additionally, the dispersion contains 0.25% Sorbic Acid, NF and small mounts of Sodium Hydroxide, NF. It is an aqueous acrylic polymer dispersion containing 30% solids. The active polymer is Methacrylic Acid Copolymer Type C; CAS number [25212-88-8]. The mean molecular weight is 250,000. The vapor pressure at 20°C is about 18 mmHg.

The dried polymer film is insoluble in gastric fluid and highly impermeable to water. Eudragit L30D-55 cannot be found in the current USP/NF; however, methacrylic acid copolymer type C is listed in the current USP/NF.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

---

g. Additives (continued)

xi. Triethyl Citrate, NF

Triethyl Citrate (TEC) is also known as: ethyl citrate and the ethylester of citric acid. It is commonly used in Pharmaceutical and food preparations.

Triethyl Citrate (TEC) is a colorless, odorless, oily liquid. It is slightly soluble in water (6.5% at 25°C) and is miscible with alcohol and ether. The empirical formula of triethyl citrate is HOC(CH2COOC2H5)2COOC2H5 with a molecular weight of 276.0. The CAS number for TEC is [77-93-0] The vapor pressure at 107°C is 1 mmHg. Triethyl Citrate (TEC) meets current USP specifications.

g. Additives (continued)

xii. Colloidal Silicon Dioxide, NF

Colloidal Silicon Dioxide is also known as silica and silicic anhydride.

Colloidal Silicon Dioxide is a bluish-white, very light, odorless, amorphous powder. It is insoluble in water and organic solvents. Its empirical formula is SiO_2, to give a molecular weight of 60.08. The CAS number is [112945-52-5]. The vapor pressure is negligible. Colloidal Silicon Dioxide meets current USP specifications.

---

g. Additives (continued)

xiii. Hard Gelatin Capsules

Two capsule sizes are used, for the manufacturer of Carbamazepine Sustained-Release Capsules, Zero Elongated and One Elongated. Both are composed of Gelatin, USP. Gelatin is derived from collagen by hydrolytic action forming a heterogeneous mixture of water-soluble proteins of high average molecular weight. The CAS number is [9000-70-8]. The vapor pressure is negligible.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

---

h. Impurities

No impurities are found in the product at greater than 1%.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

6. Introduction of Substances into the Environment

---

a. Substances Expected to be Emitted

i. Intermediate Pellet Manufacture

Pharmavene contracts Manufacturing Site 1 to produce Carbamazepine Immediate-Release Pellets, Carbamazepine Sustained-Release Pellets and Carbamazepine Enteric-Release Pellets. The only notable emissions during production are solid waste and negligible aqueous emissions. See Table I in the Confidential Appendix 3, page 198.

ii. Encapsulation and Packaging Production

Pharmavene contracts Manufacturing Site 2 to encapsulate and package the Carbamazepine Sustained-Release Capsule drug product. The only significant emission during encapsulation and packaging is solid waste. See Table II in the Confidential Appendix 3, page 198.

iii. Quality Control Testing of Intermediate Pellet and Finish Drug Product

Pharmavene's Quality Control Laboratory (Quality Control Site 1), performs release testing on Intermediate Pellets and the Carbamazepine Sustained-Release Capsule drug product. The only notable emission during testing is solid waste. See Table III and IV in the Confidential Appendix 3, page 198.

The total waste emission (intermediate pellets and encapsulation and packaging) is displayed in Table V in the Confidential Appendix 3, page 198.

6. Introduction of Substances into the Environment

b. Controls Exercised

i. Manufacturing Site 1

Manufacturing Site 1 utilizes carbamazepine drug substance and all excipients except Gelatin Capsules to produce intermediate pellets. The production of intermediate pellets involves the manufacture of three distinct pellets: an immediate-release, a sustained-release, and an enteric-release pellet. The immediate-release pellets are utilized to produce the sustained and enteric-release pellets. Manufacturing Site 1 EPA ID number is MDD091818930.

During the various processing steps at Manufacturing Site 1 dust particles are collected through a series of building ventilation systems and equipment exhaust air sources. They are directed to collection filters that display a 99.97% efficiency rating. The dust particles are collected periodically and removed from the unit and disposed of off-site as non-hazardous waste. Waste water treatment is comprised of an on-site pretreatment system consisting of four 2000 gallon neutralization tanks. Waste water is adjusted to a pH of 6 to 10. The waste water is then filtered through a plate frame filter to remove any remaining solids. Treated effluent is discharged to the sewerage system under the provision of the local County Public Sewerage System in compliance with Waste Water Discharge Permit No. 93-196-K.

In general, all solid waste both filtered and dry solids are collected and sent off-site to be placed into a secure Class A land fill by, Laidlaw Environmental Services (TS), Inc., in compliance with all Federal, State and Local Regulations. An inspection report certifying compliance of Laidlaw with the state rules and regulations is included in Section 6.c.i, page 026.

b. Controls Exercised (continued)

ii. Manufacturing Site 2

The intermediate pellets are encapsulated and packaged at Manufacturing Site 2. A description of the controls used to limit substance emissions is provided in this section. Manufacturing Site 2 EPA identification number is NJD 098258726.

The immediate-release, sustained-release and enteric-release pellets are individually blended. The blender is a closed system consisting of : air seals to aid in protection against product infiltration and hinged sealed access covers which help to produce a dust-tight operation. Blended pellets are discharged and sealed in appropriate containers.

The immediate-release, sustained-release and enteric-release pellets are then encapsulated individually and sequentially. The entire encapsulator process is equipped with a hood which has glass doors fitted with safety devices that stop the machine and a vac-u-max dust collector. Capsules are then passed through a capsule weight check system. The encapsulated drug product is then packaged into HDPE bottles. Air emissions from the encapsulation and packaging of carbamazepine drug product are collected through a series of filter dust collectors. Particulate emissions are regulated by air permits issued by the state's Department of Environmental Protection and Energy.

The dust collectors are periodically cleaned. The processing equipment is vacuumed, before being cleaned. Product dust, solid encapsulation packaging waste, both filtered and dry, are collected and sent off-site for disposal at Ogden Martin Systems of Fairfax, Inc., Lorton, Va. in compliance with all Federal, State and Local Regulations. The solid waste is destroyed by a high efficiency (99.97%) incinerator. The residual solids produced from incineration are disposed of into an

6. Introduction of Substances into the Environment

b. Controls Exercised (continued)

adjacent single clay lined leachate collection system.

Only small amounts of substances are discharged into the water used in cleaning of the equipment. This waste water is directed to an on-site pretreatment system consisting of a 5000 gallon neutralization tank. Waste water is adjusted to a pH of 6 to 10. Waste water effluent from the tank is discharged to the local POTW in compliance with Sewer Connection Permit No. 32405702. The expiration date is 04/18/98. The surface water discharge is in compliance with the state's of Environmental Protection Agency Permit No. NJ0035572. The permit expires 01/31/2000.

b. Controls Exercised (continued)

iii. Quality Control Site 1

Intermediate and finished drug product samples are tested at Quality Control Site 1. Controls used to limit the facilities substance emissions are discussed in this section. Quality Control Site 1 Drug Establishment identification number is 1124762/BLT.

In the testing of the intermediates and the finished drug product Carbamazepine, the following tests are performed: appearance, residual ignition, moisture, pellet size distribution, average content and non-parent peaks, identification, uniformity of dosage units and dissolution.

The particulate emissions based on the these tests are insignificant. The facility is equipped with a series of filter dust collectors. The filters display a 40% efficiency rating. The filters are collected, cleaned, and replaced, monthly. No air permit is required.

All wastewater is directed to an on-site 500 gallon neutralization tank. The wastewater is adjusted to a pH of 6 to 7. Wastewater emissions generated by testing are nominal. Treated effluent is discharged to the Montgomery County Public Sewerage System. The facility shall comply with the Federal general pretreatment regulations in 40 CFR Part 403 and the applicable national categorical pretreatment standards set out in 40 CFR Subchapter N Parts 401 through 471 upon promulgation and all applicable Federal, State, or local requirements or standards. No permit is required.

Except for dissolution testing waste, all emissions generated by the quality control site 1 will be solid. All solid residuals are sent off-site for disposal. The waste is disposed of off-site in accordance with the all local, state and federal environmental regulatory requirements by Advanced Environmental Technical Services. The solid waste is to be placed in a secure leachate collection system.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

i. Manufacturing Site 1

Manufacturing Site 1 strives to comply with all OSHA, MOSHA and EPA regulations. Manufacturing Site 1 is routinely inspected by these organizations. Manufacturing Site 1 was inspected by MOSHA in 1993. (See Confidential Appendix 7, pages 206-207 for the letter of compliance from Manufacturing Site 1). All employees at Manufacturing Site 1 are provided with protective equipment including lab coats, safety glasses, safety shoes, respirators and gloves.

Laidlaw Environmental Services (TS), Inc., Laurel, Maryland is the solid waste disposal service contracted by Manufacturing Site 1. Laidlaw Environmental Services (TS) is in compliance with all local, state and federal waste disposal regulations, including E.P.A. regulations. (See pages 027-031 for compliance reports pertaining to Laidlaw Environmental Services).

Confidential Appendix 4 lists all permits which apply to the process conducted at the Manufacturing Site 1. (See page 201).

EPA

ACKNOWLEDGEMENT OF NOTIFICATION OF REGULATED WASTE ACTIVITY *(VERIFICATION)*

This is to acknowledge that you have filed a Notification of Regulated Waste Activity for the installation located at the address shown in the box below to comply with Section 3010 of the Resource Conservation and Recovery Act *(RCRA)*. Your EPA Identification Number for that installation appears in the box below. The EPA Identification Number must be included on all shipping manifests for transporting hazardous wastes; on all Annual Reports that generators of hazardous waste, and owners and operators of hazardous waste treatment, storage and disposal facilities must file with EPA; on all applications for a Federal Hazardous Waste Permit; and other hazardous waste management reports and documents required under Subtitle C of RCRA.

EPA ID. NUMBER

MDD980559653

INSTALLATION ADDRESS

CAIDLAW ENVIRONMENTAL SERVICES (TS) I
3527 WHISKEY BOTTOM ROAD
LAUREL , MD 20724
BRIGHTON HOOVER FAC MGR

3527 WHISKEY BOTTOM ROAD
LAUREL , MD 20724

EPA Form 8700-12A (6-90)

027

MARYLAND DEPARTMENT OF THE ENVIRONMENT
2500 Broening Highway • Baltimore, Maryland 21224
(410) 631-3000

Parris N. Glendening
Governor

Jane T. Nishida
Secretary

INSPECTION REPORT:

RE: FI-96-1-25-AA-003

FACILITY NAME:	Laidlaw Environmental Services (TS), Inc. 3527 Whiskey Bottom Road Laurel, Maryland 20724 301-953-9583
EPA ID # :	MDD980554653
CHS PERMIT #:	A-207

Date of inspection: 1/25/96

Date of report: 1/29/96

I. Representatives Present:

1) Mr. William Baker
Environmental Compliance Officer
Laidlaw Environmental Services (TS), Inc.

2) Mr. Steve Dolina
Local Resource Manager
Laidlaw Env. Ser. (TS), Inc.

3) Ms. Isis Otero
Public Health Engineer
MDE/WAS/Hazardous Waste Enforcement Division
410-631-3400

II. Purpose:

The objective of my visit was to conduct a compliance evaluation inspection (CEI). The CEI verified compliance with RCRA pursuant to 40CFR 260 - 268, and the Code of Maryland regulations (COMAR) 26.13. This inspection consisted of a records review followed by a facility tour.

III. Introduction:

Laidlaw Environmental (TS) Services is a permitted hazardous waste management facility located in Laurel, Maryland. Laidlaw is allowed to store a maximum of 150,000 gallons of hazardous wastes and may perform the "solidification" treatment specified by permit A-207.

IV. Hazardous Waste Generation:

Laidlaw Environmental Services handles waste generated by off-site institutions such as: hospitals, universities, industries including manufacturing, research, development facilities, and government agencies (see permit A-207).

V. Hazardous Waste Management:

Laidlaw stores CHS at the following containment areas: T1, T2, T3, & T4. Areas T1 and T2 are located at the loading dock. Areas T1 and T2 are subdivided into six bays, each. The remaining areas are part of the warehouse portion of the facility and are subdivided into four bays, each. A description of the CHS storage areas follows:

A) 90 day accumulation areas:

- None

B) Satellite accumulation areas:

- Laboratory: Wastes generated during laboratory procedures are stored in a 30 gallon drum (size has been estimated). Wastes are emptied every night. No violations were noted.

C) Areas T1 and T2:

- No violations were observed during this visit.

D) Areas T3 and T4:

- This inspector observed the following during the trailer inspection: 1) deficient aisle space at one of the trailers, and 2) A crushed drum. Actions were taken to correct these conditions.

VI. Records Keeping:

A) Manifests:

Manifests were reviewed at random. The review included the following :

1) Incoming manifests: MDC0538974, MDC0545445, MDC0559002, MDC0540643, MDC0545640, MDC0545666, MDC0534401, and MDC0519142.

2) Outgoing manifests: AR609032, MDC0422772, LAA3233084, and LAA32330833.

No manifest discrepancies were noted.

B) Waste Analysis Plan:

Laidlaw kept a copy of the MDE-approved waste analysis plan, as required by permit A-207.

C) General Inspection Requirements:

The facility maintains a daily inspection log. Daily inspection logs are reviewed by the facility's operations manager at the end of each week. Inspection logs for years 93, 94, and 95 were reviewed. Inspection records appeared to be in compliance with permit requirements.

D) Personnel Training Records:

Personnel training records were selected at random. Records for Mr. Steve Dolina and Mr. Haught Shawn were reviewed. The records appeared to be in compliance with the requirements of COMAR 26.13.05.02G.

E) Contingency Plan/ Emergency Procedures:

The facility maintains a copy of the MDE approved contingency plan, as required by permit A-207.

F) Annual Reports:

The facility submits annual reports as required by COMAR 26.13.05.05F. The records are very large due to the commercial nature of this facility. Annual hazardous waste reports can be retrieved and reviewed at the facility's computers. This inspector reviewed the 1994 hazardous waste report on site. The 92 and 93 reports could not be reviewed on site due to technical difficulties.

VII. Pollution Minimization/ Other Observations:

VIII. Violations:

-N/A

IX. Enforcement Actions:

- N/A

X. Schedule of Compliance:

- N/A

Inspector: Isis Otero
Isis Otero- PHE

Date: 2/9/96

Facility
Representative _____

Date: _____

c. Citation of and Statement of Compliance with Applicable Emission Requirements (continued)

ii. Manufacturing Site 2

Manufacturing Site 2 endeavors to be in compliance with OSHA and the state's Department of Health regulations. Manufacturing Site 2 provides personnel with appropriate personal protective equipment including safety glasses, safety shoes, protective clothing, respirators (Powered Air Purifying Respirators) and gloves. Facilities and equipment are designed to reduce personnel exposure to product dust through engineering and operating controls. Industrial hygiene monitoring was carried out by OSHA and the state's Department of Health. Future monitoring will be carried out at appropriate intervals.

All waste is transported by Freehold Cartage, Inc. or United Enviro. Systems and is disposed by Ogden Martin Systems of Fairfax, Inc., Lorton, Virginia. These services are contracted by Manufacturing Site 2 and are in accordance with all state and federal regulations. Copies of letters of compliance from Freehold Cartage, Inc., and United Enviro Systems is in Confidential Appendix 8 on page 208.

Confidential Appendix 5 lists all permits which apply to the process conducted at Manufacturing Site 2, see page 202.

6. Introduction of Substances into the Environment

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c. Citation of and Statement of Compliance with Applicable Emission Requirements (continued)

iii. Raw Material Site 1

Raw Material Site 1 is the manufacturer of Carbamazepine, USP. A letter from Raw Material Site 1 certifying that the manufacturing facilities are in compliance with all local and national environmental laws is found in Confidential Appendix 9, see page 217.

c. Citation of and Statement of Compliance with Applicable Emission Requirements (continued)

iv. Quality Control Site 1

It is the intention of Quality Control Site 1 to comply will all local, state and federal regulations. (See Confidential Appendix 11, page 221 for the letter of compliance from Quality Control Site 1). All employees at Quality Control Site 1 are provided with lab coats, safety glasses and gloves. Facilities and equipment are designed to reduce personnel danger through engineering and operating controls.

The solid waste disposal company contracted by Quality Control Site 1 is Advanced Environmental Technical Services (AETS), Flanders, New Jersey. AETS is in compliance with all local, state, and federal regulations, including EPA and DOT regulations. Advanced Environmental Technical Services (AETS) EPA number is NJD980536593. A letter of compliance from Advanced Environmental Technical Services is in Confidential Appendix 11 on page 222.

For permit information pretaining to the process conducted at Quality Control Site 1, see Confidential Appenidx 5, page 203.

6. Introduction of Substances into the Environment

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d. Discussion of the effect of Approval on Compliance with Current Emission Requirements

i. Manufacturing Site 1

The facility was granted an air emission permit, 13-8-0018N, for its fluid bed dryer by the Department of the Environment. The air waste emission at this facility for the production of this product was estimated to be zero (0) kilograms per year. The approval of the product will have no effect upon compliance with current emission limits.

The facility wastewater treatment is comprised of an on-site pretreatment system consisting of four 2000 gallon neutralization tanks. Waste water is adjusted to a pH of 6 to 10. The waste water is then filtered through a plate frame filter to remove any remaining solids. The facility has a wastewater discharge permit, 93-196-K, that is associated with the manufacturing of this product. The permit requires that the wastewater discharge be maintained at a pH level between 6 to 10 and that various metal pollutant limits be maintained. Approval of this product will not exceed the limits of this permit.

This facility is not required to have a solid waste disposal permit. The facility's solid waste is disposed of off-site in accordance with the State's Department of the Environment regulatory requirements by Laidlaw Environmental Services (LES) Inc.. The solid waste emission at Manufacturing Site 1 will increase by approximately 5.0 %, based on fifth year production volume. Approval of this product will not require an immense increase in the facilities current solid waste level.

Solid waste generated at Manufacturing Site 1, is classified as non-hazardous; therefore, disposal at the off-site facility is not expected to affect compliance with current emission requirements.

6. Introduction of Substances into the Environment

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d. Discussion of the effect of Approval on Compliance with Current Emission Requirements (continued)

ii. Manufacturing Site 2

The air and water waste emissions at this facility are monitored. The facility has air quality permits for its equipment used in the manufacturing of this product. The facility also has sewage permits. Pharmavene Inc., calculates that a total of zero (0) kilograms of waste will be emitted into the air and water; therefore, approval of this product will have no effect upon compliance with current emission standards.

Solid waste disposal permit is not required for this site, due to the off-site disposal of solid waste. Off-site disposal of solid waste is performed in accordance with the Commonwealth of Virginia Department of Waste Management Solid Waste Facilities permit No. 510. The current amount of solid waste produced at Manufacturing Site 2 is approximately 100 tons per year. The solid waste production per year, based on this products estimated fifth year production volume, will increase by approximately 0.16%. Approval of this product will not require a significant increase in the facilities current solid waste level.

The off-site disposal facility residual solid waste increase from this product is estimated to be approximately 2.02% of permit limit. The approval of this product will have no effect upon compliance with Current Emission Standards.

d. Discussion of the effect of Approval on Compliance with Current Emission Requirements (continued)

iii. Quality Control Site 1

During the testing of raw materials, intermediates and drug product dosage form, the dust is collected through a series of facility filters. The filters display a 40% efficiency rating. The air emission at this facility for the testing of this product was calculated to be zero (0) kilograms per year. Particulate emissions after control are not required to be regulated by an air emission permit. Therefore, the approval of the product will have no effect upon compliance with current emission limits.

Wastewater treatment is comprised of a 500 gallon neutralization tank. Wastewater is adjusted to a pH of 6 to 7. Treated effluent is discharged to sewage system under the provision of Washington Suburban Sanitary Commission (WSSC). The facility shall comply with the Federal general pretreatment regulations in 40 CFR Part 403 and the applicable national categorical pretreatment standards set out in 40 CFR Subchapter N Parts 401 through 471 upon promulgation and all applicable Federal, State, or local requirements or standards. Only negligible amounts of wastewater emissions are discharged to sewers. No discharge Permit is required. Approval of this product will have no effect upon compliance with current emission standards.

Solid waste is sent off-site for disposal in accordance with regulatory requirements by Advanced Environmental Technical Services (AETS). The solid waste is placed into a clay liner leachate collection system. The increase in amount of solid waste is estimated to be 5.0% of the facilities existing permit level. The approval of the proposed action will have no effect upon compliance with current emission standards.

e. Expected Introduction Concentrations

In order to assess the impact on the environment of the use and disposal of Carbamazepine capsules, certain assumptions about usage patterns and amounts have been made, which are confidential. Therefore, the calculation of the Maximum Expected Emissions Concentrations (MEEC) and the calculation of the Expected Introduction Concentration (EIC) entering into the aquatic environment has been included in Confidential Appendix 6, page 204.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

7. Fate of Emitted Substances in the Environment

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a. Identification of Substance of Interest

The active ingredient, carbamazepine, is the subject of many other NDAs and has been used for many years at the same dosage levels and duration and for the same indication. This proposed action will not affect the dosage level, the duration of treatment, or the indication for carbamazepine therapy. Consequently, the environmental consequence of the use/therapy with carbamazepine will be unchanged from previous NDA approvals of carbamazepine. According to November 1995 Guidelines, Carbatrol® meets the requirements for a Tier 0 approach.

The preceding sections (4-6) support the conclusion that the proposed action does not establish that, at the levels of expected exposure, carbamazepine may be toxic to organisms in the environment. The following sections address the carbamazepine released to the air or water as a result of the proposed production. The only medium to which carbamazepine is released under this proposed action is terrestrial and such release is to landfills appropriately covered by permit which is permitted for other formulations of carbamazepine by the agency. A short summary of the fate of carbamazepine/emitted substances in the environment is more specifically addressed in the following areas.

b. Physical and Chemical Properties of Carbamazepine

Under the Freedom of Information Act, the Tegretol®-XR (Ciba-Geigy) Environmental Assessment is cited for data on the physical and chemical properties of carbamazepine including water solubility, n-Octanol/water partition coefficient, vapor pressure, ultraviolet-visible absorption spectrum, melting range and density. Section 7 of the Tegretol-XR Environmental Assessment Contains a summary of this information. Appendices 15 through 18 of the Tegretol®-XR Environmental Assessment are referenced in Section 7 for complete reports on these specifics. An entire non-confidential copy of the Tegretol®-XR Environmental Assessment is enclosed in Appendix 15.d. of this Environmental Assessment (pages 139 - 194). In summary, the following results for carbamazepine tests are listed.

i.	Water Solubility	5.1×10^{-7} M
ii.	Dissociation Constant	n/a
iii.	Partition Coefficient (log K_{ow})	1.68
	Partition Coefficient (K_{ow})	47.9
iv.	Vapor Pressure	1.33×10^{-5} Pa
v.	Others	
	$UV/VIS_{ethanol}$	209 nm max; 229 nm, 250 nm min
	$UV/VIS_{H2O\ pH\ 8.96}$	207 nm max; 229 nm, 251 nm min
	Melting Range	189 to 193°C
	$Density_{25°C}$	1.34 ±0.01 g/cm^3

7. Fate of Emitted Substances in the Environment

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c. Environmental Depletion Mechanisms

i. Carbamazepine: Metabolism and Elimination

Under the Freedom of Information Act, the Tegretol®-XR (Ciba-Geigy) Environmental Assessment Section 7.2 (page 155) is cited for information regarding the fate of carbamazepine administered to patients.

ii. Terrestrial Ecosystems

According to the physical and chemical properties listed in Section 7 of this Environmental Assessment, relatively small quantities of carbamazepine will be escaping the landfill environment and will largely remain in the solid form.

d. Expected Environmental Concentration (EEC)

According to format item 6e, Carbatrol® meets the requirement for a Tier 0 approach, and the expected environmental concentration is minimal.

e. Summary

According to format item 6e, Carbatrol® meets the requirement for a Tier 0 approach, and the expected environmental concentration is minimal.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

8. Environmental Effects of Released Substances

The environmental effect of product use on organisms in the environment is addressed specifically in Section 8 of the Tegretol®-XR Environmental Assessment, which has been obtained through the Freedom of Information Act and a copy of which is enclosed in Appendix 15.d. (page 139). In summary, the studies on microbial growth inhibition, acute toxicity in daphia and acute toxicity in zebra fish indicate that carbamazepine would probably not sorb significantly to the organic material in the soil or sediment or bioconcentrate substantially in aquatic organisms.

Therefore carbamazepine has a significant margin of safety. In addition, no significant toxic effects will occur due to the use and disposal of this substance.

Pursuant to the Tier 0 approach, no testing for Section 8 is needed.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

9. Use of Resources and Energy

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a. Natural Resources and Energy

i. Manufacturing Site 1

The proposed action does not require an immense increase of resources and energy above the current operating levels at the existing facilities. Manufacturing Site 1 is located on 7.55 acres of land, with FDP Phase 25-A-II zone classification, in a "New Town Industrial Use" zone area. The increase in energy activity at Manufacturing Site 1 for intermediate pellet production is nominal and not excessive. The expected product volume will not significantly increase the consumption of resources beyond levels presently experienced. The increase in energy at Manufacturing Site 1 is estimated to be approximately 0.34% of exiting levels. There is no threat to endangered species and the facility is not located on historic sites.

ii. Manufacturing Site 2

The encapsulation and packaging of the Carbamazepine drug product is carried out at Manufacturing Site 2. The facility is located on approximately 26.35 acres of land with class 5 (light industrial) zoning. The increase in energy at Manufacturing Site 2 is estimated to be only about 0.07% of existing levels. There is no threat to endangered species and the facility is not located on historic sites.

See Confidential Appendix 10, page 219, for complete information on the production facilities.

iii. Quality Control Site 1

The proposed action does not require a large increase of resources and energy above current operating levels at the exiting facility. The facility is located in an industrial area in which the surrounding area includes residential, light industry and retail business. The increase in activity at the listed quality control site is estimated to be about 0.42% of existing level.s. No significant impact upon existing levels is anticipated at this level of increase. There is no threat to endangered species and the facility is not located on a historical site.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

9. Use of Resources and Energy

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a. Natural Resources and Energy (continued)

See Confidential Appendix 10, page 219, for complete information on Quality Control facility.

iii. Transportation

The amount of energy utilized to transport Carbamazepine goods and waste is nominal. The amount of diesel gasoline used is estimated to be 69.4 gallons per month.

iv. Use and Disposal

The use of carbamazepine will be expected to result in wastes disposed of in waste treatment facilities nationwide. The annual amount will be the production amount, disregarding the small portion dispensed to patients and unused. This amount will not have a significant effect on the POTWs nationwide, where the inflow amounts to about 80 x 1012 lbs per year. Thus, the addition of small amounts of carbamazepine to these POTWs across the country will not have a significant effect on them, either their operation or the content of their effluent.

b. Endangered or Threatened Species

Transport, use and disposal of the carbamazepine will take place across the entire United States, but the amounts in any one location will be small enough so as to have no significant effect on any endangered or threatened species in that location.

c. The National Register of Historic Places

Transport, use and disposal of the material will be nationwide, but the amounts of any one location will not affect any historic place, assuming that existing highways, landfills, and POTWs have all been cited with reference to the impact on historic places in the area.

IV. ENVIRONMENTAL ASSESSMENT (CONTINUED)

10. Mitigation Measures

No further mitigation measures are required other than those listed in Section 6., page 021. To our knowledge and ability maximum efforts are taken to landfill excess materials from the production of Carbamazepine Sustained-Release Capsules.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

11. Alternatives to the Proposed Action

There are no alternatives to the proposed action described herein. No environmental consequences will result from the proposed action.

The approximate patient population for this drug is 2 million. It is a substantial benefit to the population at large to have this drug/dosage form available. Additional information to support our conclusion can be found in the Tegretol®-XR Environmental Assessment obtained through the Freedom of Information Act, included in Appendix 15.d., page 139.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

12. List of Preparers

---

a. Beth A. Burnside, Ph.D.
Associate Director Pharmaceutical Development
Pharmavene, Inc.

b. Richard A. Couch, Ph.D.
Senior Vice President, Pharmaceutical Sciences
Pharmavene, Inc.

c. Gary Flamm, Ph.D.
Flamm Associates

d. Edward M. Rudnic, Ph.D.
Senior Vice President, Development and Technical Operations
Pharmavene, Inc.

e. Sandra E. Wassink
Director Pharmaceutical Technology
Pharmavene, Inc.

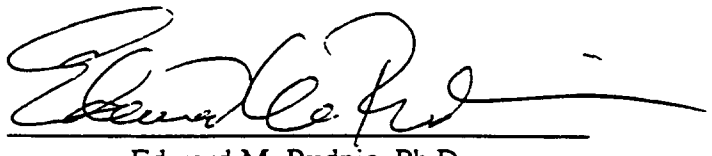
A curriculum vitae, documenting the qualifications and credentials for each of the contributors to this environmental assessment is provided in Appendix 15.c.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

13. Certification

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm or agency responsible for reparation of the EA.

The undersigned official certifies that the EA summary document contained non-confidential information and acknowledges that this information will be made available to the public is accordance with 40 CFR § 1506.6.



10/2/96

Edward M. Rudnic, Ph.D.
Senior Vice President
Development and Technical Operations

Date

ENVIRONMENTAL ASSESSMENT (CONTINUED)

14. References

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a. Aboul-Ehien and Al-Badr; "*Carbamazepine*" in "*Analytical Profiles of Drug Substances, vol 9*". Academic Press, Inc., 1980 pp. 87-106.

b. N.F. Billups; S.M. Billups. In "*American Drug Index*", Facts and Comparisons, A Wolters Kluwer Company, J.B. Lippincott Company, 1993.

c. S. Budavari; M.J. O'Neil; A. Smith. In "*The Merck Index*", Merck and Co., Inc., Rahway, NJ, USA 1989.

d. "*Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements*", Center for Drug Evaluation and Research (CDER), November, 1995.

e. G.K. McEvoy; K. Litvak; O.H. Welch. In "*American Hospital Formulary Service Drug Information*", the American Society of Hospital Pharmacists, Inc., Bethesda, MD, 1993.

f. "*The United States Pharmacopeia 23/The National Formulary 18*" The United States Pharmacopeial Convention, Inc., Rockville, MD 1995.

ENVIRONMENTAL ASSESSMENT (CONTINUED)

15. Appendices

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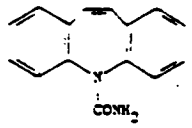
a. Merck Index

1783. Carbamazepine. *5H-Dibenz[b,f]azepine-5-carboxamide*; 5-carbamoyl-*5H*-dibenz[*b,f*]azepine; G 32883; Biston; Calepsin; Carbelan; Epitol; Finlepsin; Sirtal; Stazepine; Tegretal; Tegretol; Teiesmin; Timonil. $C_{15}H_{12}N_2O$; mol wt 236.26. C 76.25%, H 5.12%, N 11.86%, O 6.77%. Prepn: Schindler, U.S. pat. 2,948,718 (1960 to Geigy). Metabolism: P. L. Morselli, A. Frigerio, *Drug Metab. Rev.* 4, 97 (1975). Review of pharmacokinetics in man: L. Bertilsson, *Clin. Pharmacokinet.* 3, 128-143 (1978); S. Pynnönen, *Ther. Drug Monit.* 1, 409-431 (1979). Toxicity: E. G. Stenger, F. C. Rouiet, *Med. Exp.* 11, 191 (1964). Comprehensive description: H. Y. Aboul-Enein, A. A. Al-Badr in *Analytical Profiles of Drug Substances* vol. 9, K. Florey, Ed. (Academic Press, New York, 1980) pp 87-106.



Crystals from abs ethanol – benzene, mp 190-193°. Sol in alcohol, acetone, propylene glycol. Practically insol in water. LD_{50} orally in mice, rats: 3750, 4025 mg/kg (Stenger, Rouiet).

THERAP CAT: Analgesic. Anticonvulsant.

1961. Cellulose. $(C_6H_{10}O_5)_n$. Polysaccharide with the glucose units linked as in cellobiose. Chief constituent of the fiber of plants; cotton is the purest natural form, contg about 90%. Rayon is regenerated cellulose. Books: C. Doree, *The Methods of Cellulose Chemistry* (Chapman & Hall, London, 1947); T. Lieser, *Kurzes Lehrbuch der Cellulosechemie* (Gebrüder Borntraeger, Berlin, 1953); S. D. Antonovskii, *Chemistry of Wood and Cellulose* (Vsesoyuz. Zaochnyi Lesotekh Instit., Leningrad, 1954); E. Ott *et al.*, *Cellulose and Cellulose Derivatives*, vols. 1-3 (Interscience, New York, 1954, 1955). *Reviews*: Several authors in *Encyclopedia of Polymer Science and Technology* vol. 3, N. M. Bikales, Ed. (Interscience, New York, 1965) pp 131-539; Shafizadeh, *Pure Appl. Chem.* 35, 195-208 (1973); A. F. Turbak *et al.* in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 5 (Wiley-Interscience, New York, 3rd ed., 1979) pp 70-89. Comprehensive review on constitution, conformation, size of molecule, fine structure and superstructure: H. Krassig, *Papier (Darmstadt)* 33, 9-20 (1979).

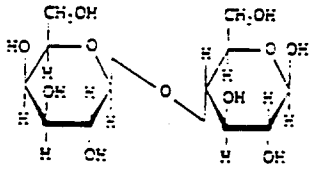
White substance. Practically insol in water or other usual solvents, but is dissolved by concd soln of zinc chloride, by ammoniacal copper hydroxide soln; also by caustic alkali with carbon disulfide.

Microcrystalline form. *Avicel*. Prepn and manuf of crystallite cellulosic aggregates: Battista, *Ind. Eng. Chem.* 42, 502 (1950); Battista, Smith, U.S. pats. 2,978,446 and 3,141,-875 (1961 to Am. Viscose and 1964 to FMC). Non-fibrous powder. Particle shape: rigid rods. Refractive index: 1.55. Bulk density: 18-19 lb/cubic foot. Practically insol, but dispersible in water; partially sol with swelling in dil alkali; practically insol in and resistant to dil acid; practically insol and inert in organic acids.

USE. Fibrous form is the basic material for the textile and paper industries. Nitrated it yields nitrocellulose used for manuf of explosives, collodion, lacquers. Basic material also for cellulose acetate, cellulose xanthate. Also used in chromatography and as ion exchange material especially in the form of derivatives such as *DEAE-cellulose* (diethylaminoethyl cellulose) and ECTEOLA-cellulose, *q.v.* Microcrystalline forms of cellulose are used as combination binder-disintegrants in tableting, as separatory medium in thin-layer and column chromatography. Colloidal cellulose particles aid in stabilization and emulsification of liquid and foam systems. May be used as pure cellulose raw-material. Incorporation of cellulose crystallite aggregates in foods to reduce caloric content: Battista, U.S. pat. 3,023,104 (1962 to American Viscose); also used in food industry as stabilizer, thickener, texturizer.

NK 5221. **Lactose.** *4-O-β-D-Galactopyranosyl-D-glucose; 4-(β-D-galactosido)-D-glucose;* milk sugar. $C_{12}H_{22}O_{11}$; mol wt 342.30. C 42.10%, H 6.48%, O 51.42%. Present in milk of mammals: human 6.7%; cow's 4.5%. Milk at body temp contains lactose as an equilibrium mixture of 2 parts of α-lactose and 3 parts of β-lactose. By-product of the cheese industry, produced from whey: Davis. *Can. Dairy and Ice Cream J.* 19, 52 (1940); *Milk Trade Gaz.* 12, 4 (1941); F. Ullmann. *Encyklopädie der Technischen Chemie.* VII, 579 (2nd ed., 1931). Structure and configuration: Zemplén. *Ber.* 59, 2402 (1926); Levene, Sobotka, *J. Biol. Chem.* 71, 471 (1926); Levene, Wintersteiner, *ibid.* 75, 315 (1927); Haworth, Long, *J. Chem. Soc.* 1927, 544; Hudson, *J. Am. Chem. Soc.* 52, 1712 (1930); Hassid, Ballou in *The Carbohydrates.* W. Pigman, Ed. (Academic Press, New York, 1957) p 495. Synthesis: Haskins *et al., J. Am. Chem. Soc.* 64, 1852 (1942).

Reviews: Whittier, *Chem. Rev.* 2, 85-125 (1926); *J. Dairy Sci.* 27, 505-537 (1944); Weisberg, *ibid.* 37, 1106-1115 (1954); L. A. W. Theiwall, *Dev. Food Carbohyd.* 2, 275-326 (1980).



α-Lactose monohydrate, is the usual milk sugar and the lactose of pharmacy. Monoclinic sphenoidal crystals from water. Faintly sweet taste. Stable in air, but readily absorbs odors. d^{20} 1.53. Becomes anhydrous at 120°. mp 201-202° (rapid heating). Shows mutarotation. $[\alpha]_D^{20}$ +92.6° → +83.5° (10 min.) → +69° (50 min) → +52.3° (22 hrs, c = 4.5). The final value is obtained instantly in the presence of a trace of NH_3. U.S.P. requires +52.2° to +52.5° (c = 10). One gram dissolves in 5 ml water, in 2.6 ml boiling water; very slightly sol in alcohol. Insol in chloroform, ether. Ka at 16.5° = 6.0×10^{-13}. d_4^{20} of aq solns calcd for the monohydrate: 5.2% = 1.018; 10.2% = 1.038; 20.0% = 1.078; 30.2% = 1.122; 50.9% = 1.226; 60.8% = 1.281; 69.1% = 1.330.

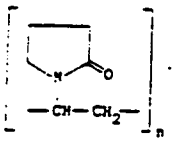
β-Lactose. $C_{12}H_{22}O_{11}$. Obtained by crystallizing concd solns of α-lactose above 93.5°. Somewhat sweeter than the α-form. $[\alpha]_D^{20}$ +34° (3 min) → +39° (6 min) → +46° (1 hr) → +52.3° (22 hrs). One gram dissolves in 2.2 ml water at 15°, in 1.1 ml boiling water. After a few days crystals of the less sol α-monohydrate appear from satd solns.

On hydrolysis with 2% H_2SO_4 or with emulsin lactose yields 1 mol D-glucose and 1 mol D-galactose. Reduces Fehling's soln.

USE: Both forms of lactose are employed, with the α-form predominating: as a nutrient in preparing modified milk and food for infants and convalescents (Whittier, "Lactose and Its Utilization," *loc. cit;* review with 327 ref). In baking mixtures. Pharmaceutic aid (tablet and capsule diluent). To produce lactic acid fermentation in ensilage and food products. As chromatographic adsorbent in analytical chemistry. In culture media. For many other uses see the comprehensive review by Weisberg "Recent Progress in the Manufacture and Use of Lactose," *loc. cit.*

THERAP CAT (VET): Added to cow's milk for feeding orphan foals.

7700. Povidone. ***1-Ethenyl-2-pyrrolidinone polymers; 1-vinyl-2-pyrrolidinone polymers:*** poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvinylpyrrolidone; polyvidone; P.V.P.; RP 143; Kollidon; Peregal ST; Periston; Plasdone; Plasmosan; Protagent; Subtosan. Vinisil. Solns are known as *Haemodyn.* Produced commercially as a series of products having mean mol wts ranging from about 10,000 to 700,000. Prepared by Reppe's process: 1,4-butanediol obtained in the Reppe butadiene synthesis is dehydrogenated over copper at 200° forming γ-butyrolactone; reaction with ammonia yields pyrrolidone. Subsequent treatment with acetylene gives the vinyl pyrrolidone monomer. Polymerization is carried out by heating in the presence of H_2O_2 and NH_3. *Cf.* P. B. reports 163; 1288; also DeBell *et al. German Plastics Practice* (Springfield, 1946); Hecht, Weese. *Münch. Med. Wochenschr.* 1943, 11; Weese. *Naturforschung & Medizin* 62, 224 (Wiesbaden, 1948), and the corresp vol. of *FIAT Review of German Science.* Monographs: General Aniline and Film Corp., *PVP* (New York, 1951); W. Reppe. *Polyvinylpyrrolidon* (Monographie zu "*Angewandte Chemie*" no. 66, Weinheim/Bergstr., 1954).



Family yellow solid resembling albumin, but does not give the reactions of albumin. Sol in water giving a colloidal soln. Also sol in alcohol, chloroform. Practically insol in ether. A 3.5% soln develops an osmotic pressure of about 400 mm water.

USE: Pharmaceutic aid (dispersing and suspending agent). Proposed as clarifying agent in wines.

8587. **Sodium Lauryl Sulfate.** *Sulfuric acid monododecyl ester sodium salt:* sodium dodecyl sulfate: SDS: Inum. $C_{12}H_{25}NaO_4S$: mol wt 288.38. C 49.98%. H 8.74%. Na 7.97%. O 22.19%. S 11.12%. $CH_3(CH_2)_{10}CH_2OSO_3Na$. Anionic detergent: prepd by sulfation of lauryl alcohol, followed by neutralization with sodium carbonate: A. Lottermoser, F. Stoll, *Kolloid-Z.* 63, 50 (1933). Surfactant properties: J. Powney, C. C. Addison, *Trans. Faraday Soc.* 33, 1244 (1937); E. E. Dreger *et al., Ind. Eng. Chem.* 36, 610 (1944). Use in electrophoretic sepn and mol wt estimation of proteins: A. L. Shapiro *et al., Biochem. Biophys. Res. Commun.* 28, 815 (1967); K. Weber, M. Osborn, *J. Biol. Chem.* 244, 4406 (1969); of glycopolypeptides: B. S. Leach *et al., Biochemistry* 19, 5734 (1980). Toxicity study: A. I. T. Walker *et al., Food Cosmet. Toxicol.* 5, 763 (1967). Review of toxicology: Ch. Glozhuber, *Arch. Toxicol.* 32, 245-270 (1974).

White or cream-colored crystals, flakes, or powder. Faint odor of fatty substances. Smooth feel. Neutral reaction. One gram dissolves in 10 ml water, giving an opalescent soln. Lowers the surface tension of aq solns. Emulsifies fats. LD_{50} orally in rats: 1288 mg/kg (Walker).

USE: Wetting agent, detergent, esp in the textile industry. Electrophoretic separation of proteins and lipids. Ingredient of toothpastes.

9011. Talc. Talcum: French chalk. The lumps are also known as *soapstone* or *steatite*. Finely powdered native hydrous magnesium silicate.

White to grayish-white, very fine odorless, crystalline powder; unctuous, and adheres readily to the skin. Insol in water, cold acids or in alkalies.

USE: Dusting powder, either alone or with starch or boric acid, for medicinal and toilet prepns; excipient and filler for pills, tablets and for dusting tablet molds; clarifying liquids by filtration. As pigment in paints, varnishes, rubber; filler for paper, rubber, soap; in fireproof and cold-water paints for wood, metal and stone; lubricating molds and machinery; glove and shoe powder; electric and heat insulator.

2328. Citric Acid. *2-Hydroxy-1,2,3-propanetricarboxylic acid; β-hydroxytricarballylic acid.* $C_6H_8O_7$, mol wt 192.12. C 37.51%, H 4.20%, O 58.29%. Widely distributed in plants and in animal tissues and fluids. Produced by mycological fermentation on an industrial scale using crude sugar solns, such as molasses and strains of *Aspergillus niger*. See review by Von Loesecke, *Chem. & Eng. News* 23, 1952 (1945); Schweiger, U.S. pat. 2,970,084 (1961 to Miles Labs.); Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 275-279. Also extracted from citrus fruits (lemon juice contains 5 to 8%) and from pineapple waste. *Reviews:* Wilson, *Chem. & Met. Eng.* 29, 787 (1923); Browne, *Ind. Eng. Chem.* 13, 81 (1921); Warneford, Hardy, *ibid.* 17, 1283 (1925); E. F. Bouchard, E. G. Merritt in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 6 (Wiley-Interscience, New York, 3rd ed., 1979) pp 150-179. Toxicity: Gruber, Halbeisen, *J. Pharmacol. Exp. Ther.* 94, 65 (1948).

Anhydr form, mp 153°. Crystals are monoclinic holohedra and crystallize from hot concd aq soln. d 1.665. At 25°, pK_1 3.128; pK_2 4.761; pK_3 6.396. Bates, Pinching, *J. Am. Chem. Soc.* 71, 1274 (1949). Soly in water: 54.0% w/w at 10°; 59.2% at 20°; 64.3% at 30°; 68.6% at 40°; 70.9% at 50°; 73.5% at 60°; 76.2% at 70°; 78.8% at 80°; 81.4% at 90°; 84.0% at 100°.

Monohydrate, orthorhombic crystals from cold aq solns. Pleasant, sour taste. d 1.542. Monohydrate crystals lose water of crystn in dry air or when heated at about 40 to 50°, slightly deliquescent in moist air. Softens at 75°, mp ~100°. pH of 0.1*N* soln = 2.2. Densities of aq soln (15°/15°): 10% = 1.0392; 20% = 1.0805; 30% = 1.1244; 40% = 1.1709; 50% = 1.2204; 60% = 1.2738. Soly in g/100 g satd soln: ether 2.17; chloroform 0.007; amyl alcohol 15.43; amyl acetate 5.98; ethyl acetate 5.28. Soly at 19° in g/100 g solvent: methanol 197; propanol 62.8. LD_{50} i.p. in rats: 975 mg/kg (Gruber, Halbeisen).

Pharmaceutical Incompatibilities: Potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, sulfides. Dilute aq solns may ferment on standing.

Barium salt heptahydrate, $C_{12}H_{10}Ba_3O_{14}.7H_2O$, *barium citrate.* Powder. Loses all H_2O at 150°. Sol in 1750 parts water; freely sol in dil HCl or HNO_3; practically insol in alcohol.

Ethyl ester, $C_{12}H_{20}O_7$, *ethyl citrate, triethyl citrate.* Bitter, oily liq. d^{20} 1.137. bp_{760} 294°; $bp_{1.0}$ 127°. Viscosity at 25°: 35.2 cps. Pour pt ~10°. n_D^{20} 1.4455. Soly: water ~6.9%; peanut oil 0.8%. Misc with alc, ether.

USE: Acidulant in beverages, confectionery, effervescent salts, in pharmaceutical syrups, elixirs, in effervescent powders and tablets, to adjust the pH of foods and as synergistic antioxidant, in processing cheese. Used in beverages, jellies, jams, preserves and candy to provide tartness. In the manuf of alkyd resins; in esterified form as plasticizer, foam inhibitor. In the manuf of citric acid salts. As sequestering agent to remove trace metals. As mordant to brighten colors; in electroplating; in special inks; in analytical chemistry for determining citrate-soluble P_2O_5; as reagent for albumin, mucin, glucose, bile pigments.

THERAP CAT: Component of anticoagulant citrate solns (citrate dextrose soln, citrate phosphate dextrose soln; citric acid syrup).

7545. Polyethylene Glycol. *α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl);* macrogol; PEG; Carbowax; Jeffox; Nycoline; Pluracol E; Poly-G; Polyglycol E; Solbase. Liquid and solid polymers of the general formula $H(OCH_2CH_2)_nOH$, where *n* is greater than or equal to 4. In general, each PEG is followed by a number which corresponds to its average mol wt. Synthesis: Fordyce, Hibbert, *J. Am. Chem. Soc.* 61, 1905, 1910 (1939). *Reviews: Glycols:* G. O. Curme, Jr., F. Johnston, Eds., A.C.S. Monograph Series no. 114 (Reinhold, New York, 1952) pp 176-202; Kastens in *High Polymers,* H. Mark *et al.*, Eds., vol. 13 entitled *Polyethers,* part 1 (Interscience, New York, 1963) pp 169-189, 274-291; G. M. Powell, III in *Handbook of Water-Soluble Gums & Resins,* R. L. Davidson, Ed. (McGraw-Hill, New York, 1980) pp 18/1-18/31.

Clear, viscous liquids or white solids which dissolve in water forming transparent solns. Sol in many organic solvents. Readily sol in aromatic hydrocarbons. Only slightly sol in aliphatic hydrocarbons. Do not hydrolyze or deteriorate on storage, will not support mold growth. Polyethylene glycols are compds of low toxicity: Smyth *et al., J. Am. Pharm. Assoc., Sci. Ed.* 39, 349 (1950). Toxicity data (PEG 400): W. Bartsch *et al., Arzneimittel-Forsch.* 26, 1581 (1976).

Polyethylene glycol 200, average value of *n* is 4, mol wt range 190-210. Viscous, hygroscopic liq; slight characteristic odor; d_{25}^{25} 1.127. Viscosity (210°F): 4.3 centistokes. Supercools upon freezing.

Polyethylene glycol 400, average value of *n* between 8.2 and 9.1, mol wt range 380–420. Viscous, slightly hygroscopic liq; slight characteristic odor; d_{25}^{25} 1.128, mp 4–8°. Viscosity (210°F): 7.3 centistokes. LD_{50} orally in rats: 30 ml/kg (Bartsch).

Polyethylene glycol 600, average value of *n* between 12.5 and 13.9, mol wt range 570-630. Viscous, slightly hygroscopic liq; characteristic odor; d_{25}^{25} 1.128, mp 20-25°. Viscosity (210°F): 10.5 centistokes.

Polyethylene glycol 1500, average value of *n* between 29 and 36, mol wt range 1300-1600. White, free-flowing powder; d_{25}^{25} 1.210, mp 44–48°. Viscosity (210°F): 25-32 centistokes.

Polyethylene glycol 4000, average value of *n* between 68 and 84, mol wt range 3000-3700. White, free-flowing powder or creamy-white flakes; d_{25}^{25} 1.212, mp 54-58°. Viscosity (210°F): 76-110 centistokes. LD_{50} orally in rats (divided doses): 59 g/kg (Smyth).

Polyethylene glycol 6000, average value of *n* between 158 and 204, mol wt range 7000-9000. Powder or creamy-white flakes; d_{25}^{25} 1.21, mp 56-63°. Viscosity (210°F): 470-900 centistokes. LD_{50} orally in rats: > 50 g/kg (Smyth).

USE: As water-soluble lubricants for rubber molds, textile fibers, and metal-forming operations. In food and food packaging. In hair prepns, in cosmetics in general. Pharmaceutic aid (ointment and suppository base). As a stationary phase in gas chromatography. Also in water paints, paper coatings, polishes and in the ceramics industry. *Caution: Solvent action on some plastics!*

THERAP CAT (VET): Ointment base.

15. Appendices

9951. Water. Hydrogen oxide. H_2O: mol wt 18.016. H 11.19%. O 88.81%. *Reviews*: N. E. Dorsey, *Properties of Ordinary Water-Substance*, A.C.S. Monograph Series no. 81, (Reinhold, New York, 1940) 673 pp; D. Eisenberg, W. Kauzmann, *The Structure and Properties of Water* (Oxford University Press, New York, 1969) 296 pp; Ebsworth *et al.*, in *Comprehensive Inorganic Chemistry* vol. 2, J. C. Bailar, Jr. *et al.*, Eds. (Pergamon Press, Oxford, 1973) pp 741-747.

Liquid. Temp of max density 3.98°. $d^{3.98}$ 1.000000 g/ml (0.999972 g/cc). d_4^{25} 0.997. d^0 (ice) 0.917 g/cc; d_4^0 (liq) 0.999868. Density tables: Bigg, *Brit. J. Appl. Phys.* 18, 521 (1967); Kell, *J. Chem. Eng. Data* 12, 66 (1967). Expands on freezing. mp 0°. bp 100°. One liter satd vapor weighs 0.5974 g at 100° and 760 mm. Crit temp 374.2°; crit pressure 218 atm. Sp. heat (liq; 14°) 1.000 cal/g/°C. Latent heat of fusion: 1.436 kcal/mole. Latent heat of vaporization: 9.717 kcal/mole. n_D^{20} 1.3330. Dielectric const (0°) 87.740. Dipole moment (25°) in benzene 1.76; in dioxane 1.86. Ionization const for pure water only: K (25°) 1.008×10^{-14}; at moderate concn of solutes (e.g. 1.0*M* KOH): K (25°) 0.971×10^{-14}. The most universal solvent known.

Pyrogen-free water (water for injection) is distilled water rendered free of fever-producing proteins (bacteria and their metabolic products). Method of prepn: Ishizuka *et al.*, *C.A.* 49, 15177 (1955). *See also* Pyrogens.

124. **Acrylic Acid.** *2-Propenoic acid;* vinylformic acid. $C_3H_4O_2$; mol wt 72.06. C 50.00%, H 5.60%, O 44.40%. $CH_2{=}CHCO_2H$. Prepd by hydrolysis of acrylonitrile: Kasiuba, *J. Am. Chem. Soc.* 67, 1227 (1945) or by oxidation of acrolein: U.S. pats. 1,911,219 (1933 to Rohm & Haas); 2,288,566 (1942 to Acrolein Corp.); 2,341,339 (1944 to Distillers). Various other syntheses, *see Org. Syn.* coll. vol. III, 30-34 (1955). *Review:* J. W. Nemec, W. Bauer in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 1 (Wiley-Interscience, New York, 3rd ed., 1978) pp 330-354.

Corrosive liquid; acrid odor and fumes. d_4^{16} 1.0621. mp 14°. bp 141.0°; bp_{400} 122.0°; bp_{200} 103.3°; bp_{100} 86.1°; bp_{40} 66.2°; bp_{10} 39.0°; bp_4 27.3°. n_D^{20} 1.4224. Flash pt, open cup: 155°F (68°C). K at 25° = 5.6×10^{-5}. Miscible with water, alc, ether. Polymerizes readily in the presence of oxygen. LD_{50} orally in rats: 2.59 g/kg, H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* 23, 95 (1962).

USE: In the manuf of plastics. *Caution:* Strong irritant.

15. Appendices

As published in the Röhm Tech, Inc. literature, Eudragit RL30D is manufactured by Röhm GmbH (Darmstadt, Germany) and is supplied by Röhm Tech, Inc. (Malden, MA).

PHARMA POLYMERS

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RÖHM TECH INC
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Since 1907

A Company of the Hüls Group

Specifications and test methods for

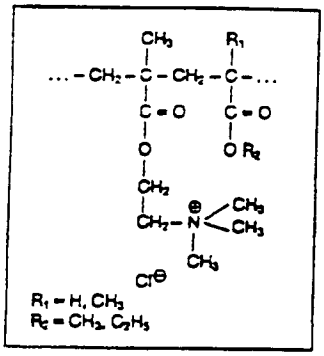
EUDRAGIT® RL 30 D
EUDRAGIT® RS 30 D

"Ammonio Methacrylate Copolymer" USP/NF

Standards Sheet

Chemical structure

EUDRAGIT RL 30 D and RS 30 D are aqueous dispersions of co-polymers of acrylic and methacrylic acid esters with a low content in quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable. The copolymers are described in USP/NF as "Ammonio Methacrylate Copolymer, Type A" (EUDRAGIT RL) and "Type B" (EUDRAGIT RS).



The average molecular weight is approx. 150,000.

Where the properties described hereafter are the same for both types we refer to EUDRAGIT RL/RS.

Commercial form

Aqueous dispersions containing 30 % dry substance.

Milky-white liquids of low viscosity with a faint characteristic odour.

EUDRAGIT RL/RS 30 D contain 0.25 % sorbic acid Ph. Eur./NF as a preservative as well as small quantities of sodium hydroxide Ph. Eur./NF.

Properties

The polymers meet the requirements of USP/NF.

Solubility
The aqueous dispersions are miscible with water in any desired proportion, the milky-white appearance being retained. 1 part EUDRAGIT RL/RS 30 D dissolves in 5 parts acetone, ethanol or isopropyl alcohol to give clear to slightly cloudy solutions.

When mixed with methanol in a ratio of 1:5, EUDRAGIT RL 30 D dissolves completely, EUDRAGIT RS 30 D only partially. When mixed with 1N sodium hydroxide in a ratio of 1:2, neither dispersion dissolves.

Film formation
10 g EUDRAGIT RL/RS 30 D are mixed with 0.6 g triethyl citrate. When poured onto a glass plate, a transparent film forms upon evaporation of the water.

15. Appendices

As published in the Röhm Tech, Inc. literature, Eudragit RL30D is manufactured by Röhm GmbH (Darmstadt, Germany) and is supplied by Röhm Tech, Inc. (Malden, MA). (continued)

Dry substance
28.5 - 31.5 %

1 g dispersion is dried in an oven for 3 hrs at 110 °C according to Ph. Eur., "Loss on drying," method d. After drying, the dispersion must form a transparent film.

Assay
EUDRAGIT RL 30 D
Alkali value: 27.5 - 37.1 mg KOH per g dry substance.

EUDRAGIT RS 30 D
Alkali value: 16.5 - 22.3 mg KOH per g dry substance.

The alkali value (AV) is defined similarly to the acid value. It states how many mg KOH are equivalent to the basic groups contained in 1 g dry substance (DS).

The alkali value is determined according to Ph. Eur. "Potentiometric titration."

2 g EUDRAGIT RL 30 D or 4 g EUDRAGIT RS 30 D are dried in vacuo in an oven for 30 minutes at 90 °C. Subsequently the sample is dissolved in 75 ml anhydrous acetic acid within about 30 minutes at approx. 50 °C. After the solution has cooled down, 25 ml copper (II) acetate solution (0.6 % solution in anhydrous acetic acid) are added and 0.1N perchloric acid is used as the titrant.

$$AV\ (mg\ KOH/g\ DS) = \frac{ml\ 0.1\ N\ HClO_4 \cdot 561}{sample\ weight\ (g) \cdot DS\ (\%)}$$

Viscosity
max. 200 mPa · s

The viscosity of the dispersion is measured by means of a Brookfield viscometer (spindle 1/30 rpm/ 20 °C).

Relative density
d_{20}^{20}: 1.047 - 1.057

The relative density of the dispersion is determined according to Ph. Eur., "Relative density."

Coagulum content
A stainless steel wire cloth with a mesh size of 0.125 mm (mesh number 125, ISO) is accurately weighed. 100 g EUDRAGIT RL/RS 30 D are filtered through this cloth, which is then washed with water until a clear filtrate is obtained, dried to constant weight at 105 °C and weighed to determine the filtration residue.

Standard limit:
max. 1,000 mg $\hat{=}$ 1 %

Purity

1. **Residue on ignition:** max. 0.5 % according to Ph. Eur., "Sulphated ash" or USP, "Residue on ignition."
2. **Heavy metals:** max. 20 ppm according to Ph. Eur., "Heavy metals," method C or USP, "Heavy metals," method II.
3. **Arsenic:** max. 2 ppm according to USP, "Arsenic," method II.

1 g EUDRAGIT RL/RS 30 D is used for the tests.

4. **Residual monomers:** max. 80 ppm ethyl acrylate max. 20 ppm methyl methacrylate, according to USP/NF, "Ammonio Methacrylate Copolymer."
5. **Microbial count:** max. 1,000 CFU/g; Salmonella, E. coli, S. aureus, Ps. aeruginosa not detectable in 10 g.

The test is performed according to Ph. Eur., "Microbial contamination of products not required to comply with the test for sterility" or "Tests for specified microorganisms."

15. Appendices

As published in the Röhm Tech, Inc. literature, Eudragit RL30D is manufactured by Röhm GmbH (Darmstadt, Germany) and is supplied by Röhm Tech, Inc. (Malden, MA). (continued)

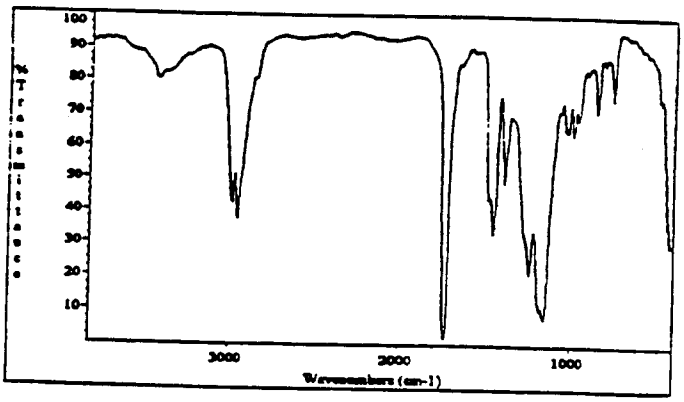
Identity testing

Proof of identity is established by IR spectroscopy on a dry EUDRAGIT RL or RS film approx. 15 µm thick.

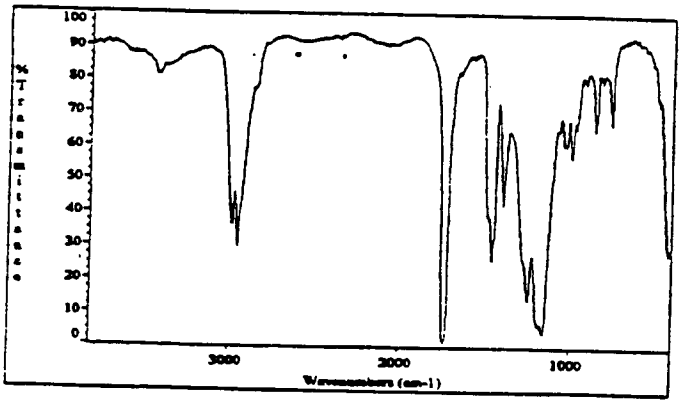
The film is obtained by applying one drop of EUDRAGIT RL/RS 30 D to a glass plate and covering it with a water-resistant crystal disc (AgCl, KRS 5). By lightly pressing on and removing the crystal disc, a clear film is obtained after a drying time of approx. 15 minutes at 60 °C.

The figures show the characteristic bands of the ester groups at 1,150 - 1,190, 1,240 and 1,270 cm^{-1}, as well as the C = O ester vibration at 1,730 cm^{-1}. In addition, CH_x vibrations can be discerned at 1,385, 1,450, 1,475 and 2,950 - 3,000 cm^{-1}.

EUDRAGIT RL 30 D



EUDRAGIT RS 30 D



Detection in dosage forms

The dosage forms are extracted using the solvents listed under "solubility." If necessary after crushing. Insoluble solid substances are removed by filtration or centrifugation. The clear filtrate is boiled down and the residue identified by infra-red spectroscopy.

Storage and handling

Store at temperatures between 5 and 25 °C. EUDRAGIT RL/RS 30 D should not be exposed to frost or to temperatures exceeding 30 °C.

Avoid contamination during sampling. Containers that have been opened for use should be closed again immediately and their contents used up within the next few weeks.

Stability

At least 18 months from date of certificate.

As published in the Röhm Tech, Inc. literature, Eudragit L30D is manufactured by Röhm GmbH (Darmstadt, Germany) and is supplied by Röhm Tech, Inc. (Malden, MA).

EUDRAGIT® L 30 D-55

Standards Sheet

Aqueous acrylic polymer dispersion

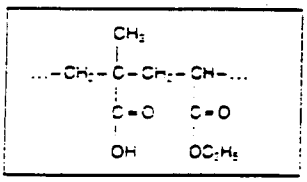
for enteric film coatings
soluble in intestinal fluid as of pH 5.5

"Methacrylic Acid Copolymer" USP/NF

Specifications and test methods for EUDRAGIT L 30 D-55

Chemical structure

EUDRAGIT L 30 D-55 is the aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The solid substance derived from EUDRAGIT L 30 D-55 is described in USP/NF as "Methacrylic Acid Copolymer, Type C."



The ratio of the free carboxyl groups to the ester groups is approx. 1:1.

The average molecular weight is 250,000.

Commercial form

Aqueous dispersion with 30 % dry substance. Milky-white liquid of low viscosity with a faint characteristic odour.

The dispersion contains 0.7 % Sodium Lauryl Sulphate Ph. Eur./NF and 2.3 % Polysorbate 80 Ph. Eur./NF on solid substance, as emulsifiers.

Properties

The solid substance meets the requirements of USP/NF.

Solubility
The dispersion is miscible with water in any desired proportion, the milky-white appearance being retained. A clear or slightly cloudy, viscous solution is obtained by mixing 1 part EUDRAGIT L 30 D-55 with 5 parts acetone. The same results are obtained by mixing with ethanol or isopropyl alcohol; initially, the polymer is precipitated, but then dissolves again in the excess organic solvent.

A clear or slightly cloudy liquid is obtained by mixing 1 part EUDRAGIT L 30 D-55 with 2 parts 1 N sodium hydroxide.

15. Appendices

As published in the Röhm Tech, Inc. literature, Eudragit L30D is manufactured by Röhm GmbH (Darmstadt, Germany) and is supplied by Röhm Tech, Inc. (Malden, MA). (continued)

Film formation
10 g EUDRAGIT L 30 D-55 are mixed with 0.3 g triethyl citrate. When the dispersion is poured onto a glass plate, a clear film forms upon evaporation of the water.

Dry substance
28.5 - 31.5 %

Approx. 1 g of the dispersion is dried in an oven for 5 hrs at 110 °C, according to Ph. Eur., "Loss on drying," method d. The dispersion must form a clear film after drying.

Assay
46.0 - 50.6 % methacrylic acid units on dry substance (DS)
Acid value: 300 - 330 mg KOH per g dry substance

The assay is performed according to Ph. Eur., "Potentiometric titration." Approx. 0.8 g EUDRAGIT L 30 D-55 is diluted with 100 ml water. Sodium hydroxide (NaOH) 0.5N is used as the titrant. Under the same conditions, a blank value is determined. 1 ml 0.5N NaOH corresponds to 43.045 mg methacrylic acid units.

Methacrylic acid units (%) on DS:

$$\frac{\text{ml 0.5 N NaOH} \cdot 430.45}{\text{sample weight (g)} \cdot \text{DS (\%)}}$$

The acid value (AV) states how many mg KOH are required to neutralise the acid groups contained in 1 g dry substance.

AV (mg KOH/g DS) = methacrylic acid units (%) · 6.517

Viscosity
max. 15 mPa · s

The viscosity of the dispersion is determined by means of a Brookfield viscometer (UL adapter/ 30 rpm/20 °C).

pH
2.0 - 3.0

The pH of the dispersion is determined according to Ph. Eur., "Potentiometric determination of pH."

Relative density
d_{20}^{20}: 1.062 - 1.072

The relative density of the dispersion is determined according to Ph. Eur., "Relative density."

Coagulum content
A stainless steel wire cloth with a mesh size of 0.09 mm (mesh number 90, ISO) is accurately weighed. 100 g EUDRAGIT L 30 D-55 are filtered through this cloth, which is then washed with water until a clear filtrate is obtained, dried to constant weight at 105 °C and weighed to determine the filtration residue.

Standard limit:
max. 1.000 mg ≙ 1 %

Purity

1. **Sulphated ash:** max. 0.12 % according to Ph. Eur., "Sulphated ash" or USP, "Residue on ignition."

2. **Heavy metals:** max. 20 ppm according to Ph. Eur., "Heavy metals," method C or USP, "Heavy metals", method II.

3. **Arsenic:** max. 2 ppm according to USP, "Arsenic," method II.

1 g EUDRAGIT L 30 D-55 is used for the tests.

4. **Residual monomers:** max. 100 ppm according to USP/NF, "Methacrylic Acid Copolymer."

   The test is performed on 120 mg EUDRAGIT L 30 D-55.

5. **Microbial count:** max. 1,000 CFU/ml; Salmonella, E. coli, S. aureus, Ps. aeruginosa not detectable in 10 g.

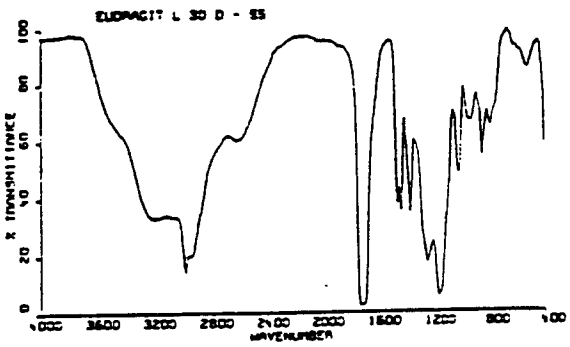
   The test is performed according to Ph. Eur., "Microbial contamination of products not required to comply with the test for sterility" or "Tests for specified micro-organisms."

As published in the Röhm Tech, Inc. literature, Eudragit L30D is manufactured by Röhm GmbH (Darmstadt, Germany) and is supplied by Röhm Tech, Inc. (Malden, MA). (continued)

Identity testing

Proof of identity is established by IR spectroscopy on a dry EUDRAGIT L 30 D-55 film approx. 15 µm thick. To obtain the film, a few drops of the dispersion are placed on a glass plate, which is then covered with a water-resistant crystal disc (AgCl, KRS 5). By lightly pressing on and then removing the crystal disc, a clear film is obtained after a drying period of about 15 minutes at 60 °C.

The figure shows the characteristic bands of the C = O vibrations of the carboxylic acid groups at 1,705 cm^{-1} and of the esterified carboxylic groups at 1,735 cm^{-1}, as well as further ester vibrations at 1,150 - 1,180 and 1,250 - 1,270 cm^{-1}, strongly associated OH vibrations in the range of 2,500 - 3,500 cm^{-1} as well as CH_x vibrations at 1,385, 1,450, 1,475 and 2,940 - 2,990 cm^{-1}.



Detection in dosage forms

The dosage forms are extracted using the solvents listed under "solubility," if necessary after crushing. Insoluble solid substances are removed by filtration or centrifugation. The clear filtrate is boiled down and the residue identified by infrared spectroscopy.

Storage and handling

Store at temperatures between 5 and 25 °C. EUDRAGIT L 30 D-55 must not be exposed to frost or to temperatures exceeding 30 °C.

Avoid contamination during sampling. Containers that have been opened for use should be closed again immediately and the content used up within the next few weeks.

Stability

At least 18 months from date of certificate.

8440. Silicon Dioxide. *Silica:* silicic anhydride. O_2Si: mol wt 60.09. O 53.25%. Si 46.75%. SiO_2. Occurs in nature as *agate, amethyst, chalcedony, cristobalite, flint, quartz, sand, tridymite. Reviews:* Several authors in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 18 (Interscience, New York, 2nd ed., 1969) pp 46-111; Rochow in *Comprehensive Inorganic Chemistry* vol. 1, J. C. Bailar, Jr. *et al.*, Eds. (Pergamon Press, Oxford, 1973) pp 1388-1402.

Transparent, tasteless crystals, or amorphous powder. d (amorphous) 2.2. d^{α} (quartz) 2.65. Melts to a glass. Silica has the lowest coefficient of expansion by heat of any known substance. It is practically insol in water or acids, except hydrofluoric acid in which it readily dissolves forming the gas silicon tetrafluoride; it is also slowly attacked by heating with concd phosphoric acid. The crystallized forms of silica are scarcely attacked by alkalies, while the amorphous is sol, especially when finely divided. *See also* Infusorial Earth.

USE: Manuf glass, water glass, refractories, abrasives, ceramics, enamels; decolorizing and purifying oils, petroleum products, etc.; in scouring- and grinding-compounds, ferrosilicon, molds for castings; as anticaking and defoaming agent. *Caution:* Prolonged inhalation of the dust can cause fibrosis of the lung (silicosis). L. T. Fairhall, *Industrial Toxicology* (Hafner, New York, 1969) pp 105-107.

4276. Gelatin. Gelfoam: Puragel. A heterogeneous mixture of water-soluble proteins of high average mol wt. Gelatin is not found in nature but derived from collagen, q.v. by hydrolytic action. Obtained by boiling skin, tendons, ligaments, bones, etc., with water. Approx amino acid content: glycine 25.5%, alanine 8.7%, valine 2.9%, leucine 3.2%, isoleucine 1.4%, cystine and cysteine 0.1%, methionine 1.0%, phenylalanine 2.2%, proline 18.0%, hydroxyproline 14.1%, serine 0.4%, threonine 1.9%, tyrosine 0.2%, aspartic acid 6.6%, glutamic acid 11.4%, arginine 8.1%, lysine 4.1%, histidine 0.8%. The total is over 100% because water is incorporated into the molecules of the individual amino acids. Nutritionally, gelatin is an incomplete protein lacking tryptophan and contg but small amounts of other important amino acids. Review of the chemistry and structure of collagen with emphasis on its transformation to gelatin: A. Veis, *The Macromolecular Chemistry of Gelatin* (Academic Press, New York, 1964) 433 pp.

Colorless or slightly yellow, transparent, brittle, practically odorless, tasteless sheets, flakes, or coarse powder. Swells up and absorbs 5–10 times its weight of water to form a gel in solutions below 35–40°. Sol in hot water, glycerol, acetic acid. Insol in organic solvents. Amphoteric.

USE: As stabilizer, thickener and texturizer in food; manuf rubber substitutes, adhesives, cements, lithographic and printing inks, plastic compds, artificial silk, photographic plates and films, matches, light filters for mercury lamps; clarifying agent; in hectographic masters; sizing paper and textiles; for inhibiting crystn in bacteriology, for preparing cultures. Pharmaceutic aid (suspending agent; encapsulating agent; tablet binder; tablet and coating agent). *Incompat:* Tannin, formaldehyde.

THERAP CAT (VET): Plasma expander; hemostasis (sponge).

ENVIRONMENTAL ASSESSMENT (CONTINUED)

15. Appendices

b. Material Safety Data Sheets

Carbamazepine
Common Name
Cat # 09300
Unit package size: 100 mg

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

address:
12601 Twinbrook Parkway
Rockville, MD 20852 USA

emergency and information telephone calls:
(301) 881-0666

Jerome A. Halperin
Responsible Party

06-27-89
date prepared

WARNING STATEMENT
WARNING! REFERENCE STANDARD; NOT FOR HUMAN CONSUMPTION; AVOID INGESTION, INHALATION, SKIN CONTACT. FOR CHEMICAL TEST AND ASSAY USE ONLY.

SECTION 1 - IDENTITY

COMMON NAME	Carbamazepine
SYNONYMS	n/a
CAS NUMBER	298-46-4
RTECS NUMBER	HN8225000
CHEMICAL NAME	5H-Dibenz [b,f] azepine-5-carboxamide
CHEMICAL FAMILY	A Tricyclic iminostilbene derivative
THERAPEUTIC CATEGORY	Analgesic; anticonvulsant
FORMULA	$C_{15}H_{12}N_2O$

SECTION 2 - HAZARDOUS INGREDIENTS

	NAME	PERCENT	THRESHOLD LIMIT VALUE (UNITS)
PRINCIPAL HAZARDOUS COMPONENT(S)/[Chemical & Common name(s)]	Carbamazepine	Pure Material	Not Established

SECTION 3 - PHYSICAL AND CHEMICAL CHARACTERISTICS (Fire & Explosion Data)

BOILING POINT	n/a
SPECIFIC GRAVITY (H_2O = 1)	n/a
VAPOR PRESSURE (mm Hg)	n/a
PERCENT VOLATILE BY VOLUME (%)	n/a
VAPOR DENSITY (AIR = 1)	n/a
EVAPORATION RATE	n/a
SOLUBILITY IN WATER	Practically insoluble
REACTIVITY IN WATER	n/a

t = not applicable

Carbamazepine
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APPEARANCE AND ODOR	White to off-white crystalline powder; odorless
FLASH POINT	n/a
FLAMMABLE LIMITS IN AIR % BY VOLUME	LOWER n/a UPPER n/a
EXTINGUISHER MEDIA	Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials.
AUTO-IGNITION TEMPERATURE	n/a
SPECIAL FIRE FIGHTING PROCEDURES	As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing.
UNUSUAL FIRE AND EXPLOSION HAZARDS	This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electricity. When heated to decomposition material emits toxic fumes of NO_x. Emits toxic fumes under fire conditions.

SECTION 4 - PHYSICAL HAZARDS

STABILITY	( ) Unstable (X) Stable
CONDITIONS TO AVOID	Material is stable from a safety point of view.
INCOMPATIBILITY (MATERIALS TO AVOID)	n/a
HAZARDOUS DECOMPOSITION PRODUCTS	When heated to decomposition material emits toxic fumes of NO_x. Emits toxic fumes under fire conditions.
HAZARDOUS POLYMERIZATION	( ) May Occur (X) Will Not Occur

SECTION 5 - HEALTH HAZARDS

THRESHOLD LIMIT VALUE	None established
SIGNS AND SYMPTOMS OF OVEREXPOSURE	[Carbamazepine CAS RN: 298-46-4 TDLo: 160 mg/Kg/3W-Intermittent oral-man; TDLo: 1050 mg/Kg/6W-Intermittent oral-child; TDLo: 253 mg/Kg/6W-Intermittent oral-man; TDLo: 19 mg/Kg/4W-Intermittent oral-child; TDLo: 28 mg/Kg/4D-Intermittent oral-woman; TDLo: 43 mg/Kg oral-human; TDLo: 100 mg/Kg/17D-Intermittent oral-woman; LDLo: 54 mg/Kg/9D-Intermittent oral-man;

n/a = not applicable

Carbamazepine
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LDLo: 1920 mg/Kg/17W-Intermittent oral-woman;
LD_{50}: 1957 mg/Kg oral-rat;
LD_{50}: 293 mg/Kg intraperitoneal-rat;
LD_{50}: 936 mg/Kg oral-mouse;
LD_{50}: 270 mg/Kg intraperitoneal-mouse;
LD_{50}: 5620 mg/Kg oral-dog;
LD_{50}: 2680 mg/Kg oral-rabbit;
LD_{50}: 920 mg/Kg oral-guinea pig;
Reproductive Effects Data [RTECS]]

The usual adult prescribing limit for carbamazepine is 1.2 grams per day. Adverse effects include visual disturbances, mild dizziness or drowsiness, inability to coordinate muscular movements, mild nausea or vomiting, achiness, dry mouth, headache, increased sensitivity to sunlight, diarrhea, weakness, and skin rash. Overdose symptoms can be delayed for up to 3 hours following ingestion, and include severe dizziness and drowsiness, rapid heart rate, irregular, slow or shallow breathing, seizures, trembling or twitching, stupor, coma, and death. Possible allergic reaction to dust if inhaled, ingested or in contact with skin.

ACUTE — Eye, skin and/or respiratory tract irritation
CHRONIC — Possible hypersensitization

PRECAUTIONS TO CONSIDER — Persons developing hypersensitivity (anaphylactic) reactions must receive immediate medical attention. Material may be irritating to mucous membranes and respiratory tract. Although adequate and well-controlled pregnancy studies in humans have not been done, there have been reports of babies prenatally exposed to carbamazepine having small head circumference and low birth weights (FDA Pregnancy Category C) [USP DI, 9th ed. 1989] As a general rule, when handling USP Reference Standards avoid all contact and inhalation of dust, fumes, mists, and/or vapors associated with the material. Keep container tightly closed and use with adequate ventilation; wash thoroughly after handling. Individuals working with chemicals should consider all chemicals to be potentially hazardous even if their individual hazards may be uncharacterized or unknown. Persons hypersensitive to tricyclic antidepressants may

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= not applicable

Carbamazepine
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be hypersensitive to this material also.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE

Hypersensitivity to material, seizure disorders, heart problems, blood disorders, bone marrow depression, diabetes mellitus, glaucoma, hyponatremia, urinary retention, and impaired liver or kidney function.

CHEMICAL LISTED AS CARCINOGEN OR POTENTIAL CARCINOGEN

NATIONAL TOXICOLOGY PROGRAM	( ) Yes	(X) No
I.A.R.C. Monographs	( ) Yes	(X) No
OSHA	( ) Yes	(X) No

OTHER Carbamazepine is considered carcinogenic in Sprague-Dawley rats because doses of 25, 75, and 250 mg per Kg per day for 2 years caused a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males. The significance of these findings to the use of carbamazepine in humans is not known.
[USP DI 9th ed. 1989]

ACGIH		OTHER EXPOSURE	
TLV:	n/a	LIMIT(S) USED:	n/a

OSHA PERMISSIBLE EXPOSURE LIMIT: Not established

OTHER EXPOSURE LIMIT USED Not established

EMERGENCY AND FIRST AID PROCEDURES

Remove from exposure. Remove contaminated clothing. Persons developing serious hypersensitivity reactions must receive immediate medical attention. If not breathing give artificial respiration. If breathing is difficult give oxygen. Obtain medical attention. Since there is no specific antidote for carbamazepine overdose, recommended treatment is as follows:

- For large ingestions, induce vomiting or perform gastric lavage, followed by administration of activated charcoal or laxatives to reduce further absorption. Forced diuresis may accelerate elimination.
- Maintain a patent airway with tracheal intubation if necessary.

( ) = not applicable

Carbamazepine
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- For hypotension and shock, elevate the legs and administer a plasma volume expander. Use of a vasopressor may be considered if necessary.
- Administer a benzodiazepine or a barbiturate as required for seizures. The fact that these agents may aggravate respiratory depression, hypotension, and coma must be considered. Barbiturates or benzodiazepines should NOT be used if patient has taken a monoamine oxidase inhibitor within the previous 14 days.
- Dialysis is indicated only in severe poisoning associated with renal failure.
- Monitor respiration, cardiac function, blood pressure, body temperature, pupillary reflexes and kidney and bladder function for several days.

[USP DI 9th ed. 1989]

1.	INHALATION	May cause irritation of respiratory tract. Remove to fresh air.
2.	EYES	May cause irritation. Flush with copious quantities of water.
	SKIN	May cause irritation. Flush with copious quantities of water.
4.	INGESTION	May cause irritation. Flush out mouth with water. This material is slowly but almost completely absorbed from the gastrointestinal tract.

SECTION 6 - SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (SPECIFY TYPE)	NIOSH approved respirator
VENTILATION	Adequate
LOCAL EXHAUST	Recommended
MECHANICAL (GENERAL)	Recommended
OTHER	n/a
PROTECTIVE GLOVES	Rubber
EYE PROTECTION	Safety goggles
OTHER PROTECTIVE CLOTHING OR EQUIPMENT	Appropriate laboratory apparel; protect exposed skin.

n/a = not applicable

Carbamazepine
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SECTION 7 - SPECIAL PRECAUTIONS AND SPILL/LEAK PROCEDURES

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE	Store in tight container as defined in the United States Pharmacopeia. This material should be handled and stored per label and other instructions to ensure product integrity.
OTHER PRECAUTIONS	Avoid contact with eyes, skin or clothing. Avoid breathing dust or mist. Use with adequate dust control. Wash thoroughly after handling. Wear fresh clothing daily. Wash contaminated clothing before reuse. Do not permit eating, drinking or smoking near material.
STEPS TO BE TAKEN IN CASE MATERIAL IS SPILLED OR RELEASED	Wear approved respirator and chemically compatible gloves. Vacuum or sweep up spillage. Avoid dust. Place spillage in appropriate container for waste disposal. Wash contaminated clothing before reuse.
IE DISPOSAL METHODS	Dispose of waste in accordance with all applicable Federal, State and local laws.

NOTICE: The information contained herein is applicable solely to the chemical substance when used as a USP Reference Standard and does not relate to any other use of the substance described. Its use is intended by persons having technical skill and at their own discretion and risk. The information has been developed by USP staff from sources considered reliable but has not been independently verified by the USP. Therefore, the USP Convention cannot guarantee the accuracy of the information in these sources nor should the statements contained herein be considered an official expression. NO REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE is made with respect to the information contained herein.

ATTENTION:

This Product is Sold as a Reference Standard for Use In Chemical Analysis Not For Human Consumption.

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n/a = not applicable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20712

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAY 30 1997

CARBATROL (Carbamazepine SR)

200 and 300 mg capsules

NDA 20-712

Reviewer: Iftekhar Mahmood, Ph. D.

Pharmavene Inc.

Rockville, MD 20850

RETURN

MAY 30 1997

Submission Dates: December 20, 1996; February 6, 1997 and February 13, 1997.

Indication: Antiepileptic

On the above mentioned dates, Pharmavene submitted relevant informations (statistical analysis of bioequivalence studies, in-vitro/in-vivo correlation and dissolution) relating to their NDA on carbamazepine as requested by the reviewer. All these informations have been evaluated during the approval of CARBATROL. No further action is necessary at this time.

Iftekhar Mahmood, Ph.D. I Mahmood 5/29/97

RD/FT initialed by Mohammad Hossain, Ph.D. M Hossain 5/30/97

Division of Pharmaceutical Evaluation I

Office of Clinical Pharmacology and Biopharmaceutics

cc: NDA 20-712

HFD-120, HFD-860 (Mahmood, Hossain, Malinowski), CDR (Barbara Murphy)