CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-697

Name: Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg

Sponsor: Nostrum Pharmaceuticals, LLC

Approval Date: May 20, 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-697

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APPLICATION NUMBER:

ANDA 76-697

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 076697

Nostrum Pharmaceuticals, LLC
Attention: Zoia Ploscaru
Contact/Agent
1800 N. Topping Avenue
Kansas City, MO 64120

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 26, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg.

Reference is also made to your amendments dated January 19, February 23, and October 5, 2004; September 3, September 25, 2008; January 15, March 26, May 25, June 10, July 20, August 17, September 3, September 29, and October 6, 2009; and February 17, February 23, February 24, March 10, March 15, and April 1, 2011.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Carbatrol Capsules of Shire Pharmaceutical, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

Apparatus:	USP Apparatus 2 (paddle)
Rotation Speed:	75 rpm
Medium:	First 4 hours: Dilute acid, pH 1.1 with 1.8% β-cyclodextrin, 600 mL After 4 hours: 50 mM Phosphate Buffer, pH 7.5 with 1.1% β-cyclodextrin, 1000 mL
Sampling Times:	1, 4, 8 and 10 hours
Specifications:	300 mg strength: 1 hr: (b) (4) 4 hr: (b) (4); 8 hr: NLT (b) (4) 100 mg and 200 mg strength: 1 hr: (b) (4); 4 hr (b) (4) 8 hr: NLT (b) (4)

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, Shires's Carbatrol Capsules, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 5,326,570 (the '570 patent) and 5,912,013 (the '013 patent) are scheduled to expire on July 5, 2011, and June 15, 2016, respectively.

With respect to both patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg, under this ANDA. You have notified the agency that Nostrum Pharmaceuticals, LLC (Nostrum) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '570 and '013 patents was initiated against Nostrum within the statutory 45-day period in the United States District Court for the District of New Jersey [Shire LLC v. Nostrum Pharmaceuticals, Inc. and Nostrum Pharmaceuticals, LLC, Civil Action No. 03-cv-04436-MLC and 03:08-cv-03309-MLC-TJB]. You informed the agency that this litigation was resolved by means of a settlement agreement, referred to in a judgment and order entered by the court on March 22, 2010.

With respect to 180-day generic drug exclusivity for the 300 mg strength only, we note that Nostrum was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the listed patents. Therefore, with this approval, Nostrum is eligible for generic drug exclusivity for Carbamazepine Extended-release Capsules, 300 mg. The agency has determined that this exclusivity is only with respect to the '570 patent.[1] This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

[1] Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) on December 8, 2003, all references to the 180-day exclusivity provision are to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1). Nostrum has no exclusivity remaining associated with its paragraph IV certification to the '013 patent; that exclusivity was triggered (by a 2009 district court decision that the '013 patent is not infringed) and has expired. This is explained in greater detail in a letter issued by this office to another applicant; a copy of the letter has been sent to Nostrum.

Post marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

KEITH O WEBBER
05/20/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

NOSTRUM LABORATORIES, INC.

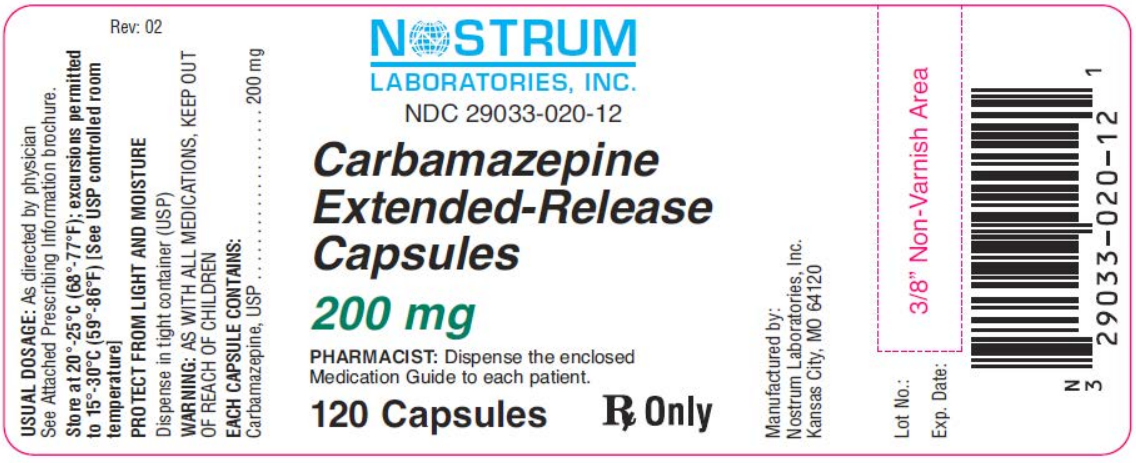
1.14.2.1 Final Carton or Container Labels

Container Labels for NLI's Extended Release Capsules, 100 mg, 30 Count

Container Labels for NLI's Extended Release Capsules, 100 mg, 120 Count

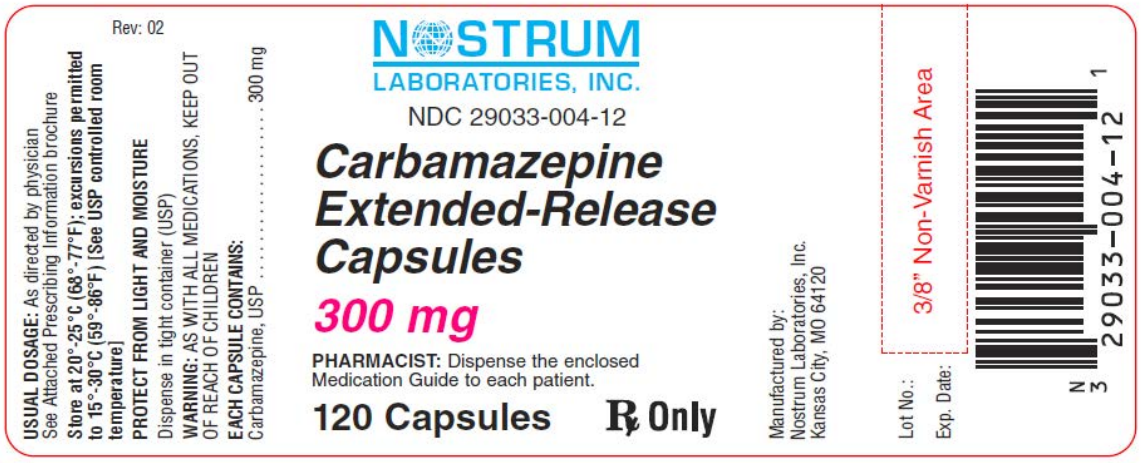
Container Labels for NLI's Extended Release Capsules, 200 mg, 30 Count

Container Labels for NLI's Extended Release Capsules, 200 mg, 120 Count



Container Labels for NLI's Extended Release Capsules, 300 mg, 30 Count

Container Labels for NLI's Extended Release Capsules, 300 mg, 120 Count



Carbamazepine Extended-Release Capsules
100 mg, and 200 mg
R_x only

WARNING

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH CARBAMAZEPINE. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE EXTENDED-RELEASE CAPSULES. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH CARBAMAZEPINE EXTENDED-RELEASE CAPSULES UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS/Laboratory Tests).

APLASTIC ANEMIA AND AGRANULOCYTOSIS

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE-CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

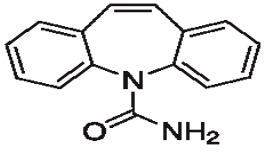
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Carbamazepine Extended Release Capsules, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Carbamazepine Extended-Release Capsules are an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as 100 mg, and 200 mg extended-release capsules of Carbamazepine, USP. Carbamazepine is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27. Its chemical name is 5H-dibenz [b,f]azepine-5-carboxamide, and its structural formula is:



Carbamazepine

Carbamazepine Extended-Release Capsules contain a single type of beads designed to provide twice daily dosing of carbamazepine.
Inactive ingredients: silicified microcrystalline cellulose, oleic acid, ethylcellulose, medium chain triglycerides, polyethylene glycols, hypromellose and sodium lauryl sulfate.

The 100 mg capsule shells contain gelatin, D&C Yellow #10, FD&C Blue #1, FD&C Yellow #6, titanium dioxide, and are imprinted with black ink; and the 200 mg capsule shells contain gelatin, D&C Yellow #10, titanium dioxide, and are imprinted with black ink.

The imprinting ink contains the following: black iron oxide, D&C Yellow # 10 Aluminum Lake, FD&C Blue #/1 Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/ Indigo Carmine Aluminum Lake, FD&C Red # 40/ Allura Red AC Aluminum Lake, propylene glycol and shellac glaze.

CLINICAL PHARMACOLOGY

In controlled clinical trials, carbamazepine has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Carbamazepine has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Carbamazepine greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Carbamazepine is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of carbamazepine, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several *in vivo* animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of carbamazepine has not been established.

Pharmacokinetics

Carbamazepine (CBZ): Taken every 12 hours, Carbamazepine Extended-Release Capsules provide steady state plasma levels comparable to immediate-release carbamazepine tablets given every 6 hours, when administered at the same total mg daily dose.

Following a single 200 mg oral extended-release dose of carbamazepine, peak plasma concentration was 1.9 ± 0.3 µg/mL and the time to reach the peak was 19 ± 7 hours. Following chronic administration (800 mg every 12 hours), the peak levels were 11.0 ± 2.5 µg/mL and the time to reach the peak was 5.9 ± 1.8 hours. The pharmacokinetics of extended-release carbamazepine is linear over the single dose range of 200-800 mg.

Carbamazepine is 76% bound to plasma proteins. Carbamazepine is primarily metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10, 11-epoxide. Since carbamazepine induces its own metabolism, the half-life is also variable. Following a single extended-release dose of carbamazepine, the average half-life range from 35-40 hours and 12-17 hours on repeated dosing. The apparent oral clearance following a single dose was 25 ± 5 mL/min and following multiple dosing was 80 ± 30 mL/min.
After oral administration of $_{14}$C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

Carbamazepine-10,11-epoxide (CBZ-E): Carbamazepine-10,11-epoxide is considered to be an active metabolite of carbamazepine. Following a single 200 mg oral extended-release dose of carbamazepine, the peak plasma concentration of carbamazepine-10,11-epoxide was 0.11 ± 0.012 µg/mL and the time to reach the peak was 36 ± 6 hours. Following chronic administration of a extended-release dose of carbamazepine (800 mg every 12 hours), the peak levels of carbamazepine-10,11-epoxide were 2.2 ± 0.9 µg/mL and the time to reach the peak was 14 ± 8 hours. The plasma half-life of carbamazepine-10,11-epoxide following administration of carbamazepine is 34 ± 9 hours. Following a single oral dose of extended-release carbamazepine (200-800 mg) the AUC and Cmax of carbamazepine- 10,11-epoxide were less than 10% of carbamazepine. Following multiple dosing of extended-release carbamazepine (800-1600 mg daily for 14 days), the AUC and Cmax of carbamazepine-10,11-epoxide were dose related, ranging from 15.7 µg.hr/mL and 1.5 µg/mL at 800 mg/day to 32.6 µg.hr/mL and 3.2 µg/mL at 1600 mg/day, respectively, and were less than 30% of carbamazepine. Carbamazepine-10,11-epoxide is 50% bound to plasma proteins.

Food Effect: The multiple dose study conducted in the fed state showed that the steady-state Cmax values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

Special Populations

Hepatic Dysfunction: The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known. However, given that carbamazepine is primarily metabolized in the liver, it is prudent to proceed with caution in patients with hepatic dysfunction.

Renal Dysfunction: The effect of renal impairment on the pharmacokinetics of carbamazepine is not known.

Gender: No difference in the mean AUC and Cmax of carbamazepine and carbamazepine-10,11-epoxide was found between males and females.

Age: Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in young children than adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age.

Race: No information is available on the effect of race on the pharmacokinetics of carbamazepine.

INDICATIONS AND USAGE

Epilepsy

Carbamazepine Extended-Release Capsules are indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe).
Patients with these seizures appear to show greater improvements than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.
Absence seizures (petit mal) do not appear to be controlled by carbamazepine (see PRECAUTIONS, General).

Trigeminal Neuralgia

Carbamazepine Extended-Release Capsules are indicated in the treatment of the pain associated with true trigeminal neuralgia. Beneficial results have also been reported in glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

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

Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated.

WARNINGS

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with carbamazepine treatment. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Carbamazepine Extended-Release Capsules should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

SJS/TEN and HLA-B*1502 Allele

Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-B*1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity.

Across Asian populations, notable variation exists in the prevalence of HLA-B*1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but higher in some groups. HLA-B*1502 is present in <1% of the population in Japan and Korea.

HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans).

Prior to initiating Carbamazepine Extended Release Capsules therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B*1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Carbamazepine Extended-Release Capsules should not be used in patients positive for HLAB*1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN (see WARNINGS and PRECAUTIONS/Laboratory Tests).

Over 90% of carbamazepine treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on Carbamazepine Extended-Release Capsules.

The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption [MPE]).

Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other anti-epileptic drugs associated with SJS/TEN. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable.

Application of HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with carbamazepine will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Patients should be made aware that Carbamazepine Extended-Release Capsules contain carbamazepine and should not be used in combination with any other medications containing carbamazepine.

Aplastic anemia and agranulocytosis

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. Data from a population-based case-control study demonstrate that the risk of developing these reactions is 5-8 times greater than in the general population. However, the overall risk of these reactions in the untreated general population is low, approximately six patients per one million population per year for agranulocytosis and two patients per one million population per year for aplastic anemia.

Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in association with the use of carbamazepine, data are not available to estimate accurately their incidence or outcome. However, the vast majority of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis. Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hematologic changes observed in monitoring of patients on carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Suicidal behavior and Ideation

Antiepileptic drugs (AEDs), including Carbamazepine Extended-Release Capsules, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.
The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 – Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Carbamazepine Extended-Release Capsules or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts or behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self harm. Behaviors of concern should be reported immediately to healthcare providers.

Usage in Pregnancy

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m2 basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

To provide information regarding the effects of in utero exposure to Carbamazepine Extended Release Capsules, physicians are advised to recommend that pregnant patients taking Carbamazepine Extended-Release Capsules enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

General

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

In patients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.
Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered.

Co-administration of carbamazepine and delavirdine may lead to loss of virologic response and possible resistance to PRESCRIPTOR or to the class of non-nucleoside reverse transcriptase inhibitors.

PRECAUTIONS

General

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

Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

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

Information for Patients

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

Patients, their caregivers, and families should be counseled that AEDs, including Carbamazepine Extended-Release Capsules, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

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

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see Warnings - Usage in Pregnancy)

If necessary, Carbamazepine Extended-Release Capsules can be opened and the contents sprinkled over food, such as a teaspoon of applesauce or other similar food products. Carbamazepine Extended-Release Capsules or their contents should not be crushed or chewed.

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

Patients, their caregivers, and families should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to taking Carbamazepine Extended-Release Capsules. See FDA approved Medication Guide.

Laboratory Tests

For genetically at-risk patients [See WARNINGS], high-resolution '*HLA-B*1502 typing*' is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Increases in total cholesterol, LDL and HDL have been observed in some patients taking anticonvulsants. Therefore, periodic evaluation of these parameters is also recommended.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone.

Hyponatremia has been reported in association with carbamazepine use, either alone or in combination with other drugs.
Interference with some pregnancy tests has been reported.

Drug Interactions

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

Agents Highly Bound to Plasma Protein:
Carbamazepine is not highly bound to plasma proteins; therefore, administration of Carbamazepine Extended-Release Capsules to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Agents that Inhibits Cytochrome P450 Isoenzymes and/or Epoxide Hydrolase:

Carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine 10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase. Therefore, the potential exists for interaction between carbamazepine and any agent that inhibits CYP3A4 and/or epoxide hydrolase. Agents that are CYP3A4 inhibitors that have been found, or are expected, to increase plasma levels of Carbamazepine Extended Release Capsules are the following:
Acetazolamide, azole antifungals, cimetidine, clarithromycin(1), dalfopristin, danazol, delavirdine, diltiazem, erythromycin(1), fluoxetine, fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, loratadine, nefazodone, niacinamide, nicotinamide, protease inhibitors, propoxyphene, quinine, quinupristin, troleandomycin, valproate(1), verapamil, zileuton.
(1) also inhibits epoxide hydrolase resulting in increased levels of the active metabolite carbamazepine 10, 11- epoxide.
Thus, if a patient has been titrated to a stable dosage of Carbamazepine Extended-Release Capsules, and then begins a course of treatment with one of these CYP3A4 or epoxide hydrolase inhibitors, it is reasonable to expect that a dose reduction for Carbamazepine Extended-Release Capsules may be necessary.

Agents that Induce Cytochrome P450 Isoenzymes:
Carbamazepine is metabolized by CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent that induces CYP3A4. Agents that are CYP inducers that have been found, or are expected, to decrease plasma levels of Carbamazepine Extended Release Capsules are the following:
Cisplatin, doxorubicin HCL, felbamate, rifampin, phenobarbital, phenytoin(2), primidone, methsuximide, and theophylline.
(2)Phenytoin plasma levels have also been reported to increase and decrease in the presence of carbamazepine, see below.

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

Agents with Decreased Levels in the Presence of Carbamazepine due to Induction of Cytochrome P450 Enzymes:
Carbamazepine is known to induce CYP1A2 and CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent metabolized by one (or more) of these enzymes. Agents that have been found, or are expected to have decreased plasma levels in the presence of Carbamazepine Extended-Release Capsules due to induction of CYP enzymes are the following:
Acetaminophen, alprazolam, amitriptyline, bupropion, buspirone, citalopram, clobazam, clonazepam, clozapine, cyclosporin, delavirdine, desipramine, diazepam, dicumarol, doxycycline, ethosuximide, felbamate, felodipine, glucocorticoids, haloperidol, itraconazole, lamotrigine, levothyroxine, lorazepam, methadone, midazolam, mirtazapine, nortriptyline, olanzapine, oral contraceptives(3), oxcarbazepine, phenytoin(4), praziquantel, protease inhibitors, quetiapine, risperidone, theophylline, topiramate, tiagabine, tramadol, triazolam, trazodone(5), valproate, warfarin(6), nefazodone, ziprasidone, and zonisamide.
(3)Break through bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.
(4)Phenytoin has also been reported to increase in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following co-medication with carbamazepine is advised.
(5)Following co-administration of carbamazepine 400mg/day with trazodone 100mg to 300mg daily, carbamazepine reduced trough plasma concentrations of trazodone (as well as meta-chlorophenylpiperazine [mCPP]) by 76 and 60% respectively, compared to precarbamazepine values.
(6)Warfarin's anticoagulant effect can be reduced in the presence of carbamazepine.

Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated (see CONTRAINDICATIONS).

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

Agents with Increased Levels in the Presence of Carbamazepine:
Carbamazepine Extended-Release Capsules increases the plasma levels of the following agents:
Clomipramine HCl, phenytoin(7), and primidone
(7)Phenytoin has also been reported to decrease in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following co-medication with carbamazepine is advised.

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

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

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

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

Because of its primary CNS effect, caution should be used when Carbamazepine Extended-Release Capsules is taken with other centrally acting drugs and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Administration of carbamazepine to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day (low dose approximately 0.2 times the maximum human daily dose of 1200 mg on a mg/m2 basis), resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Usage in Pregnancy
Pregnancy Category D (See WARNINGS)

Labor and Delivery
The effect of carbamazepine on human labor and delivery is unknown.

Nursing Mothers
Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. The concentrations of carbamazepine and its epoxide metabolite are approximately 50% of the maternal plasma concentration. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Substantial evidence of carbamazepine effectiveness for use in the management of children with epilepsy (see INDICATIONS for specific seizure types) is derived from clinical investigations performed in adults and from studies in several *in vitro* systems which support the conclusion that (1) the pathogenic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports a conclusion that the generally acceptable therapeutic range of total carbamazepine in plasma (i.e., 4-12 µg/mL) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months.
No longer term data from clinical trials is available.

Geriatric Use
No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

General: If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive patient with epilepsy may lead to seizures or even status epilepticus with its life threatening hazards.
The most severe adverse reactions previously observed with carbamazepine were reported in the hemopoietic system and skin (see BOX WARNING), and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.

The following additional adverse reactions were previously reported with carbamazepine:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) (see BOXED WARNING), pruritic and erythematous rashes, urticaria, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.
Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg/day and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills, inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion have been reported in association with carbamazepine use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with carbamazepine, nor is there evidence of psychological or physical dependence in humans.
OVERDOSAGE

Acute Toxicity
Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3- year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.
Signs and Symptoms
The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. ECG may show dysrhythmias.

Combined Poisoning:

When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with carbamazepine may be aggravated or modified.

Treatment
For the most up to date information on management of carbamazepine overdose, please contact the poison center for your area by calling 1-800-222-1222. The prognosis in cases of carbamazepine poisoning is generally favorable. Of 5,645 cases of carbamazepine exposures reported to US poison centers in 2002, a total of 8 deaths (0.14% mortality rate) occurred. Over 39% of the cases reported to these poison centers were managed safely at home with conservative care. Successful management of large or intentional carbamazepine exposures requires implementation of supportive care, frequent monitoring of serum drug concentrations, as well as aggressive but appropriate gastric decontamination.

Elimination of the Drug: The primary method for gastric decontamination of carbamazepine overdose is use of activated charcoal. For substantial recent ingestions, gastric lavage may also be considered. Administration of activated charcoal prior to hospital assessment has the potential to significantly reduce drug absorption. There is no specific antidote. In overdose, absorption of carbamazepine may be prolonged and delayed. More than one dose of activated charcoal may be beneficial in patients that have evidence of continued absorption (e.g., rising serum carbamazepine levels).

Measures to Accelerate Elimination: The data on use of dialysis to enhance elimination in carbamazepine is scarce. Dialysis, particularly high flux or high efficiency hemodialysis, may be considered in patients with severe carbamazepine poisoning associated with renal failure or in cases of status epilepticus, or where there are rising serum drug levels and worsening clinical status despite appropriate supportive care and gastric decontamination.
For severe cases of carbamazepine overdose unresponsive to other measures, charcoal hemoperfusion may be used to enhance drug clearance.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within 1 week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.
Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) $_{59}$Fe-ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.
A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patients. A low initial daily dosage with gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. The Carbamazepine Extended-Release Capsules may be opened and the beads sprinkled over food, such as a teaspoon of applesauce or other similar food products if this method of administration is preferred. Carbamazepine Extended-Release Capsules or their contents should not be crushed or chewed. Carbamazepine Extended-Release Capsules can be taken with or without meals.

Carbamazepine Extended-Release Capsules are an extended-release formulation for twice a day administration. When converting patients from immediate release carbamazepine to Carbamazepine Extended-Release Capsules, the same total daily mg dose of carbamazepine should be administered.

Epilepsy (see INDICATIONS AND USAGE)

Adults and 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, usually 800-1200 mg daily.

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 Carbamazepine Extended-Release Capsules, using a twice daily regimen. Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of Carbamazepine Extended-Release Capsules for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy: Carbamazepine Extended-Release Capsules may be used alone or 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 (see PRECAUTIONS, Drug Interactions, and Pregnancy Category D).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, start with one 200 mg capsule. This daily dose may be increased by up to 200 mg/day every 12 hours only as needed to achieve freedom from pain. Do not 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. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Carbamazepine Extended-Release Capsules are supplied as:

100 mg - Hard gelatin capsule (dark green opaque body with dark green opaque cap) printed with the "NC" / "100" logo in black ink.
Supplied in bottles of 30 . . . . . NDC 29033-019-30
Supplied in bottles of 120 . . . . . NDC 29033-019-12

200 mg - Hard gelatin capsule (yellow opaque body with yellow opaque cap) printed with the "NC" / "200" logo in black ink.
Supplied in bottles of 30 . . . . . NDC 29033-020-30
Supplied in bottles of 120 . . . . . NDC 29033-020-12

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59-86°F) [see USP Controlled Room Temperature]. PROTECT FROM LIGHT AND MOISTURE.

Manufactured by:
Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120

Rev: March 2011

MEDICATION GUIDE
CARBAMAZEPINE EXTENDED-RELEASE CAPSULES
(100 mg and 200 mg)

Rev. 00

Read this Medication Guide before you start taking Carbamazepine Extended-Release Capsules and each time you get a refill. There may be new Information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about Carbamazepine Extended-Release Capsules?

Do not stop taking Carbamazepine Extended-Release Capsules without first talking to your healthcare provider. Stopping Carbamazepine Extended-Release Capsules suddenly can cause serious problems.

Carbamazepine Extended-Release Capsules can cause serious side effects, including:

1. **Carbamazepine Extended-Release Capsules may cause rare but serious rashes that may lead to death. These serious skin reactions are more likely to happen within the first four months of Carbamazepine Extended-Release Capsules treatment but may occur at later times. These reactions can happen in anyone, but are more likely in people of Asian descent. If you are of Asian descent you may need a genetic blood test before you take Carbamazepine Extended-Release Capsules to see if you are at a higher risk for serious skin reactions with this medicine. Symptoms may include:**
    - skin rash
    - hives
    - sores in your mouth
    - blistering or peeling of the skin
2. **Carbamazepine Extended-Release Capsules may cause rare but serious blood problems. Symptoms may include:**
    - fever, sore throat or other infections that come and go or do not go away
    - easy bruising
    - red or purple spots on your body
    - bleeding gums or nose bleeds
    - severe fatigue or weakness
3. **Like other antiepileptic drugs, Carbamazepine Extended-Release Capsules may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

    Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
    - thoughts about suicide or dying
    - attempt to commit suicide
    - new or worse depression
    - new or worse anxiety
    - feeling agitated or restless
    - panic attacks
    - trouble sleeping (insomnia)
    - new or worse irritability
    - acting aggressive, being angry, or violent
    - acting on dangerous impulses
    - an extreme increase in activity and talking (mania)
    - other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop Carbamazepine Extended-Release Capsules without first talking to a healthcare provider.

Stopping Carbamazepine Extended-Release Capsules suddenly can cause serious problems.

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

What is Carbamazepine Extended-Release Capsules?

Carbamazepine Extended-Release Capsules is a medicine used to treat:

- certain types of seizures (partial, tonic-clonic, mixed)
- certain types of nerve pain (trigeminal and glossopharyngeal neuralgia).

Carbamazepine Extended-Release Capsules is not a regular pain medicine and should not be used for aches or pains.

Who should not take Carbamazepine Extended-Release Capsules?

Do not take Carbamazepine Extended-Release Capsules if you:

- have a history of bone marrow depression
- are allergic to carbamazepine or any of the ingredients in Carbamazepine Extended-Release Capsules. See the end of this Medication Guide for a complete list of ingredients in Carbamazepine Extended-Release Capsules.
- take nefazodone
- are allergic to antidepressant medications called tricyclic (TCAs).
- have taken a medicine called Monoamine Oxidase Inhibitor (MAOI) in the last 14 days.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

What should I tell my healthcare provider before taking Carbamazepine Extended-Release Capsules?

Before you take Carbamazepine Extended-Release Capsules, tell your healthcare provider if you:

- have or ever had heart problems
- have or ever had blood problems
- have or ever had liver or kidney problems
- have or ever had allergic reactions to medicines
- have or ever had increased pressure in your eye
- have or have had suicidal thoughts or actions, depression or mood problems
- have any other medical conditions
- drink grapefruit juice or eat grapefruit
- use birth control. Carbamazepine Extended-Release Capsules may make your birth control less effective. Tell your healthcare provider if your menstrual bleeding changes while you take birth control and Carbamazepine Extended-Release Capsules.
- are pregnant or plan to become pregnant. Carbamazepine Extended-Release Capsules may harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking Carbamazepine Extended-Release Capsules. You and your healthcare provider should decide if you should take Carbamazepine Extended-Release Capsules while you are pregnant.
    - If you become pregnant while taking Carbamazepine Extended-Release Capsules, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy. You can enroll in this registry by calling 1-888-233-2334.
- are breastfeeding or plan to breastfeed. Carbamazepine Extended-Release Capsules passes into breast milk. You and your healthcare provider should discuss whether you should take Carbamazepine Extended-Release Capsules or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Taking Carbamazepine Extended-Release Capsules with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take Carbamazepine Extended-Release Capsules?

- Take Carbamazepine Extended-Release Capsules exactly as prescribed. Your doctor will tell you how much Carbamazepine Extended-Release Capsules to take.
- Your healthcare provider may change your dose. Do not change your dose of Carbamazepine Extended-Release Capsules without talking to your healthcare provider.
- Do not stop taking Carbamazepine Extended-Release Capsules without first talking to your healthcare provider. Stopping Carbamazepine Extended-Release Capsules suddenly can cause serious problems. Stopping seizure medicine suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).
- Take Carbamazepine Extended-Release Capsules with or without food.
- **Do not crush, chew, or break** Carbamazepine Extended-Release Capsules or the beads inside of the capsules. But, Carbamazepine Extended-Release Capsules can be opened and sprinkled over food such as a teaspoon of applesauce. Tell your healthcare provider if you can not swallow Carbamazepine Extended-Release Capsules whole.
- If you take too much Carbamazepine Extended-Release Capsules, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking Carbamazepine Extended-Release Capsules?

- Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking Carbamazepine Extended-Release Capsules until you talk to your healthcare provider. Carbamazepine Extended-Release Capsules taken with alcohol or drugs may make your sleepiness or dizziness worse.
- Do not drive, or operate heavy machinery, or do other dangerous activities until you know how Carbamazepine Extended-Release Capsules affects you. Carbamazepine Extended-Release Capsules can slow your thinking and motor skills.

What are the possible side effects of Carbamazepine Extended-Release Capsules?

See **"What is the most important information I should know about Carbamazepine Extended-Release Capsules?"**

Carbamazepine Extended-Release Capsules may cause other serious side effects including:

- Irregular heartbeat - symptoms include:
  - Fast, slow, or pounding heartbeat
  - Shortness of breath
  - Feeling lightheaded
  - Fainting
- Liver problems - symptoms include:
  - yellowing of your skin or the whites of your eyes
  - dark urine
  - pain on the right side of your stomach area (abdominal pain)
  - easy bruising
  - loss of appetite
  - nausea or vomiting

Get medical help right away if you have any of the symptoms listed above or listed in

"What is the most important information I should know about Carbamazepine Extended-Release Capsules".

The most common side effects of Carbamazepine Extended-Release Capsules include:

- dizziness
- drowsiness
- problems with walking and coordination (unsteadiness)
- nausea
- vomiting

These are not all the side effects of Carbamazepine Extended-Release Capsules. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Carbamazepine Extended-Release Capsules?

- Store Carbamazepine Extended-Release Capsules between 59°F to 86°F (15°C to 30°C).
- Keep Carbamazepine Extended-Release Capsules out of the light.
- Keep Carbamazepine Extended-Release Capsules capsules dry.

Keep Carbamazepine Extended-Release Capsules and all medicines out of the reach of children.

General information about Carbamazepine Extended-Release Capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Carbamazepine Extended-Release Capsules for a condition for which it was not prescribed. Do not give Carbamazepine Extended-Release Capsules to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Carbamazepine Extended-Release Capsules. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Carbamazepine Extended-Release Capsules that is written for health professionals.

What are the ingredients in Carbamazepine Extended-Release Capsules?

Active ingredient: carbamazepine

Inactive ingredients: silicified microcrystalline cellulose, oleic acid, ethylcellulose, medium chain triglycerides, polyethylene glycols, hypromellose and sodium lauryl sulfate.

In addition:

- the 100 mg capsule shell contains gelatin, D&C Yellow #10, FD&C Blue # 1, FD&C Yellow #6, titanium dioxide and are imprinted with black ink
- the 200 mg capsule shell contains gelatin, D&C Yellow #10, titanium dioxide and are imprinted with black ink.

The imprinting ink contains the following: black iron oxide, D&C Yellow # 10 Aluminum Lake, FD&C Blue #1/ Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/ Indigo Carmine Aluminum Lake, FD&C Red # 40/ Allura Red AC Aluminum Lake, propylene glycol and shellac glaze.

This Medication Guide has been approved by the US Food and Drug Administration.

Manufactured by:
Nostrum Laboratories Inc.
1800 N. Topping Avenue
Kansas City, MO 64120

Rev: April 2011

Carbamazepine Extended-Release Capsules
300 mg
R_x only

WARNING

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH CARBAMAZEPINE. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE EXTENDED-RELEASE CAPSULES. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH CARBAMAZEPINE EXTENDED-RELEASE CAPSULES UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS/Laboratory Tests).

APLASTIC ANEMIA AND AGRANULOCYTOSIS

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE-CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

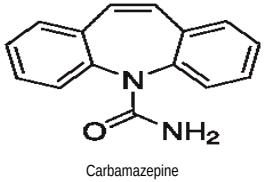
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Carbamazepine Extended Release Capsules, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Carbamazepine Extended-Release Capsules are an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as 300 mg extended-release capsules of Carbamazepine, USP. Carbamazepine is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27. Its chemical name is 5H-dibenz [b,f]azepine-5-carboxamide, and its structural formula is:



Carbamazepine

Carbamazepine Extended-Release Capsules contain a single type of beads designed to provide twice daily dosing of carbamazepine.

Inactive ingredients: silicified microcrystalline cellulose, oleic acid, ethylcellulose, medium chain triglycerides, polyethylene glycols, hypromellose and sodium lauryl sulfate.

The 300 mg capsule shells contain gelatin, D&C Red #28, FD&C Blue #1, black iron oxide, titanium dioxide, and are imprinted with black ink.

The imprinting ink contains the following: black iron oxide, D&C Yellow # 10 Aluminum Lake, FD&C Blue #1/ Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/ Indigo Carmine Aluminum Lake, FD&C Red # 40/ Allura Red AC Aluminum Lake, propylene glycol and shellac glaze.

CLINICAL PHARMACOLOGY

In controlled clinical trials, carbamazepine has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Carbamazepine has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Carbamazepine greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Carbamazepine is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of carbamazepine, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several *in vivo* animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of carbamazepine has not been established.

Pharmacokinetics

Carbamazepine (CBZ): Taken every 12 hours, Carbamazepine Extended-Release Capsules provide steady state plasma levels comparable to immediate-release carbamazepine tablets given every 6 hours, when administered at the same total mg daily dose.

Following a single 200 mg oral extended-release dose of carbamazepine, peak plasma concentration was 1.9 ± 0.3 µg/mL and the time to reach the peak was 19 ± 7 hours. Following chronic administration (800 mg every 12 hours), the peak levels were 11.0 ± 2.5 µg/mL and the time to reach the peak was 5.9 ± 1.8 hours. The pharmacokinetics of extended-release carbamazepine is linear over the single dose range of 200-800 mg.

Carbamazepine is 76% bound to plasma proteins. Carbamazepine is primarily metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10, 11-epoxide. Since carbamazepine induces its own metabolism, the half-life is also variable. Following a single extended-release dose of carbamazepine, the average half-life range from 35-40 hours and 12-17 hours on repeated dosing. The apparent oral clearance following a single dose was 25 ± 5 mL/min and following multiple dosing was 80 ± 30 mL/min.

After oral administration of $_{14}$C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

Carbamazepine-10,11-epoxide (CBZ-E): Carbamazepine-10,11-epoxide is considered to be an active metabolite of carbamazepine. Following a single 200 mg oral extended-release dose of carbamazepine, the peak plasma concentration of carbamazepine-10,11-epoxide was 0.11 ± 0.012 µg/mL and the time to reach the peak was 36 ± 6 hours. Following chronic administration of a extended-release dose of carbamazepine (800 mg every 12 hours), the peak levels of carbamazepine-10,11-epoxide were 2.2 ± 0.9 µg/mL and the time to reach the peak was 14 ± 8 hours. The plasma half-life of carbamazepine-10,11-epoxide following administration of carbamazepine is 34 ± 9 hours. Following a single oral dose of extended-release carbamazepine (200-800 mg) the AUC and Cmax of carbamazepine- 10,11-epoxide were less than 10% of carbamazepine. Following multiple dosing of extended-release carbamazepine (800-1600 mg daily for 14 days), the AUC and Cmax of carbamazepine-10,11-epoxide were dose related, ranging from 15.7 µg.hr/mL and 1.5 µg/mL at 800 mg/day to 32.6 µg.hr/mL and 3.2 µg/mL at 1600 mg/day, respectively, and were less than 30% of carbamazepine. Carbamazepine-10,11-epoxide is 50% bound to plasma proteins.

Food Effect: The multiple dose study conducted in the fed state showed that the steady-state Cmax values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

Special Populations

Hepatic Dysfunction: The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known. However, given that carbamazepine is primarily metabolized in the liver, it is prudent to proceed with caution in patients with hepatic dysfunction.

Renal Dysfunction: The effect of renal impairment on the pharmacokinetics of carbamazepine is not known.

Gender: No difference in the mean AUC and Cmax of carbamazepine and carbamazepine-10,11-epoxide was found between males and females.

Age: Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in young children than adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age.

Race: No information is available on the effect of race on the pharmacokinetics of carbamazepine.

INDICATIONS AND USAGE

Epilepsy

Carbamazepine Extended-Release Capsules are indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvements than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by carbamazepine (see PRECAUTIONS, General).

Trigeminal Neuralgia

Carbamazepine Extended-Release Capsules are indicated in the treatment of the pain associated with true trigeminal neuralgia. Beneficial results have also been reported in glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

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

Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated.

WARNINGS

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with carbamazepine treatment. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Carbamazepine Extended-Release Capsules should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

SJS/TEN and HLA-B*1502 Allele

Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-B*1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity.

Across Asian populations, notable variation exists in the prevalence of HLA-B*1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but higher in some groups. HLA-B*1502 is present in <1% of the population in Japan and Korea.

HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans).

Prior to initiating Carbamazepine Extended Release Capsules therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B*1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Carbamazepine Extended-Release Capsules should not be used in patients positive for HLAB*1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN (see WARNINGS and PRECAUTIONS/Laboratory Tests).

Over 90% of carbamazepine treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on Carbamazepine Extended-Release Capsules.

The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption [MPE]).

Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other anti-epileptic drugs associated with SJS/TEN. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable.

Application of HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with carbamazepine will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Patients should be made aware that Carbamazepine Extended-Release Capsules contain carbamazepine and should not be used in combination with any other medications containing carbamazepine.

Aplastic anemia and agranulocytosis

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. Data from a population-based case-control study demonstrate that the risk of developing these reactions is 5-8 times greater than in the general population. However, the overall risk of these reactions in the untreated general population is low, approximately six patients per one million population per year for agranulocytosis and two patients per one million population per year for aplastic anemia.

Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in association with the use of carbamazepine, data are not available to estimate accurately their incidence or outcome. However, the vast majority of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis. Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hematologic changes observed in monitoring of patients on carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Suicidal behavior and Ideation

Antiepileptic drugs (AEDs), including Carbamazepine Extended-Release Capsules, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.
The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 – Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Carbamazepine Extended-Release Capsules or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts or behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self harm. Behaviors of concern should be reported immediately to healthcare providers.

Usage in Pregnancy

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m2 basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

To provide information regarding the effects of in utero exposure to Carbamazepine Extended Release Capsules, physicians are advised to recommend that pregnant patients taking Carbamazepine Extended-Release Capsules enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

General

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

In patients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.
Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered.

Co-administration of carbamazepine and delavirdine may lead to loss of virologic response and possible resistance to PRESCRIPTOR or to the class of non-nucleoside reverse transcriptase inhibitors.

PRECAUTIONS

General

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

Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

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

Information for Patients

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

Patients, their caregivers, and families should be counseled that AEDs, including Carbamazepine Extended-Release Capsules, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

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

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see Warnings - Usage in Pregnancy)

If necessary, Carbamazepine Extended-Release Capsules can be opened and the contents sprinkled over food, such as a teaspoon of applesauce or other similar food products. Carbamazepine Extended-Release Capsules or their contents should not be crushed or chewed.

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

Patients, their caregivers, and families should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to taking Carbamazepine Extended-Release Capsules. See FDA approved Medication Guide.

Laboratory Tests

For genetically at-risk patients [See WARNINGS], high-resolution '*HLA-B*1502 typing*' is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Increases in total cholesterol, LDL and HDL have been observed in some patients taking anticonvulsants. Therefore, periodic evaluation of these parameters is also recommended.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone.

Hyponatremia has been reported in association with carbamazepine use, either alone or in combination with other drugs.
Interference with some pregnancy tests has been reported.

Drug Interactions

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

Agents Highly Bound to Plasma Protein:

Carbamazepine is not highly bound to plasma proteins; therefore, administration of Carbamazepine Extended-Release Capsules to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Agents that Inhibits Cytochrome P450 Isoenzymes and/or Epoxide Hydrolase:

Carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine 10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase. Therefore, the potential exists for interaction between carbamazepine and any agent that inhibits CYP3A4 and/or

epoxide hydrolase. Agents that are CYP3A4 inhibitors that have been found, or are expected, to increase plasma levels of Carbamazepine Extended Release Capsules are the following:
Acetazolamide, azole antifungals, cimetidine, clarithromycin(1), dalfopristin, danazol, delavirdine, diltiazem, erythromycin(1), fluoxetine, fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, loratadine, nefazodone, niacinamide, nicotinamide, protease inhibitors, propoxyphene, quinine, quinupristin, troleandomycin, valproate(1), verapamil, zileuton.
(1) also inhibits epoxide hydrolase resulting in increased levels of the active metabolite carbamazepine 10, 11- epoxide.
Thus, if a patient has been titrated to a stable dosage of Carbamazepine Extended-Release Capsules, and then begins a course of treatment with one of these CYP3A4 or epoxide hydrolase inhibitors, it is reasonable to expect that a dose reduction for Carbamazepine Extended-Release Capsules may be necessary.

Agents that Induce Cytochrome P450 Isoenzymes:
Carbamazepine is metabolized by CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent that induces CYP3A4. Agents that are CYP inducers that have been found, or are expected, to decrease plasma levels of Carbamazepine Extended Release Capsules are the following:
Cisplatin, doxorubicin HCL, felbamate, rifampin, phenobarbital, phenytoin(2), primidone, methsuximide, and theophylline.
(2)Phenytoin plasma levels have also been reported to increase and decrease in the presence of carbamazepine, see below.

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

Agents with Decreased Levels in the Presence of Carbamazepine due to Induction of Cytochrome P450 Enzymes:
Carbamazepine is known to induce CYP1A2 and CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent metabolized by one (or more) of these enzymes. Agents that have been found, or are expected to have decreased plasma levels in the presence of Carbamazepine Extended-Release Capsules due to induction of CYP enzymes are the following:
Acetaminophen, alprazolam, amitriptyline, bupropion, buspirone, citalopram, clobazam, clonazepam, clozapine, cyclosporin, delavirdine, desipramine, diazepam, dicumarol, doxycycline, ethosuximide, felbamate, felodipine, glucocorticoids, haloperidol, itraconazole, lamotrigine, levothyroxine, lorazepam, methadone, midazolam, mirtazapine, nortriptyline, olanzapine, oral contraceptives(3), oxcarbazepine, phenytoin(4), praziquantel, protease inhibitors, quetiapine, risperidone, theophylline, topiramate, tiagabine, tramadol, triazolam, trazodone(5), valproate, warfarin(6), nefazodone, ziprasidone, and zonisamide.
(3)Break through bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.
(4)Phenytoin has also been reported to increase in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following co-medication with carbamazepine is advised.
(5)Following co-administration of carbamazepine 400mg/day with trazodone 100mg to 300mg daily, carbamazepine reduced trough plasma concentrations of trazodone (as well as meta-chlorophenylpiperazine [mCPP]) by 76 and 60% respectively, compared to precarbamazepine values.
(6)Warfarin's anticoagulant effect can be reduced in the presence of carbamazepine.

Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated (see CONTRAINDICATIONS).

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

Agents with Increased Levels in the Presence of Carbamazepine:
Carbamazepine Extended-Release Capsules increases the plasma levels of the following agents:
Clomipramine HCl, phenytoin(7), and primidone
(7)Phenytoin has also been reported to decrease in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following co-medication with carbamazepine is advised.

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

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

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

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

Because of its primary CNS effect, caution should be used when Carbamazepine Extended-Release Capsules is taken with other centrally acting drugs and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Administration of carbamazepine to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day (low dose approximately 0.2 times the maximum human daily dose of 1200 mg on a mg/m2 basis), resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Usage in Pregnancy
Pregnancy Category D (See WARNINGS)

Labor and Delivery
The effect of carbamazepine on human labor and delivery is unknown.

Nursing Mothers
Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. The concentrations of carbamazepine and its epoxide metabolite are approximately 50% of the maternal plasma concentration. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Substantial evidence of carbamazepine effectiveness for use in the management of children with epilepsy (see INDICATIONS for specific seizure types) is derived from clinical investigations performed in adults and from studies in several *in vitro* systems which support the conclusion that (1) the pathogenic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports a conclusion that the generally acceptable therapeutic range of total carbamazepine in plasma (i.e., 4-12 µg/mL) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months.
No longer term data from clinical trials is available.

Geriatric Use
No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

General: If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive patient with epilepsy may lead to seizures or even status epilepticus with its life threatening hazards.
The most severe adverse reactions previously observed with carbamazepine were reported in the hemopoietic system and skin (see BOX WARNING), and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.

The following additional adverse reactions were previously reported with carbamazepine:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) (see BOXED WARNING), pruritic and erythematous rashes, urticaria, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.
Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg/day and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills, inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion have been reported in association with carbamazepine use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with carbamazepine, nor is there evidence of psychological or physical dependence in humans.
OVERDOSAGE

Acute Toxicity
Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3- year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.
Signs and Symptoms
The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. ECG may show dysrhythmias.

Combined Poisoning:
When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with carbamazepine may be aggravated or modified.

Treatment

For the most up to date information on management of carbamazepine overdose, please contact the poison center for your area by calling 1-800-222-1222. The prognosis in cases of carbamazepine poisoning is generally favorable. Of 5,645 cases of carbamazepine exposures reported to US poison centers in 2002, a total of 8 deaths (0.14% mortality rate) occurred. Over 39% of the cases reported to these poison centers were managed safely at home with conservative care. Successful management of large or intentional carbamazepine exposures requires implementation of supportive care, frequent monitoring of serum drug concentrations, as well as aggressive but appropriate gastric decontamination.

Elimination of the Drug: The primary method for gastric decontamination of carbamazepine overdose is use of activated charcoal. For substantial recent ingestions, gastric lavage may also be considered. Administration of activated charcoal prior to hospital assessment has the potential to significantly reduce drug absorption. There is no specific antidote. In overdose, absorption of carbamazepine may be prolonged and delayed. More than one dose of activated charcoal may be beneficial in patients that have evidence of continued absorption (e.g., rising serum carbamazepine levels).

Measures to Accelerate Elimination: The data on use of dialysis to enhance elimination in carbamazepine is scarce. Dialysis, particularly high flux or high efficiency hemodialysis, may be considered in patients with severe carbamazepine poisoning associated with renal failure or in cases of status epilepticus, or where there are rising serum drug levels and worsening clinical status despite appropriate supportive care and gastric decontamination.
For severe cases of carbamazepine overdose unresponsive to other measures, charcoal hemoperfusion may be used to enhance drug clearance.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within 1 week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.
Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) $_{59}$Fe-ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.
A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patients. A low initial daily dosage with gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. The Carbamazepine Extended-Release Capsules may be opened and the beads sprinkled over food, such as a teaspoon of applesauce or other similar food products if this method of administration is preferred. Carbamazepine Extended-Release Capsules or their contents should not be crushed or chewed. Carbamazepine Extended-Release Capsules can be taken with or without meals.

Carbamazepine Extended-Release Capsules are an extended-release formulation for twice a day administration. When converting patients from immediate release carbamazepine to Carbamazepine Extended-Release Capsules, the same total daily mg dose of carbamazepine should be administered.

Epilepsy (see INDICATIONS AND USAGE)

Adults and 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, usually 800-1200 mg daily.

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 Carbamazepine Extended-Release Capsules, using a twice daily regimen. Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of Carbamazepine Extended-Release Capsules for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy: Carbamazepine Extended-Release Capsules may be used alone or 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 (see PRECAUTIONS, Drug Interactions, and Pregnancy Category D).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, start with one 200 mg capsule. This daily dose may be increased by up to 200 mg/day every 12 hours only as needed to achieve freedom from pain. Do not 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. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Carbamazepine Extended-Release Capsules are supplied as:

300 mg - Hard gelatin capsule (purple opaque body with purple opaque cap) printed with the "NC" / "300" logo in black ink.
Supplied in bottles of 30 . . . . . NDC 29033-004-30
Supplied in bottles of 120 . . . . . NDC 29033-004-12

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59-86°F) [see USP Controlled Room Temperature]. PROTECT FROM LIGHT AND MOISTURE.

Manufactured by:
Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120

Rev: March 2011

MEDICATION GUIDE
CARBAMAZEPINE EXTENDED-RELEASE CAPSULES
(300 mg)

Rev. 00

Read this Medication Guide before you start taking Carbamazepine Extended-Release Capsules and each time you get a refill. There may be new Information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about Carbamazepine Extended-Release Capsules?

Do not stop taking Carbamazepine Extended-Release Capsules without first talking to your healthcare provider. Stopping Carbamazepine Extended-Release Capsules suddenly can cause serious problems.

Carbamazepine Extended-Release Capsules can cause serious side effects, including:

1. **Carbamazepine Extended-Release Capsules may cause rare but serious rashes that may lead to death. These serious skin reactions are more likely to happen within the first four months of Carbamazepine Extended-Release Capsules treatment but may occur at later times. These reactions can happen in anyone, but are more likely in people of Asian descent. If you are of Asian descent you may need a genetic blood test before you take Carbamazepine Extended-Release Capsules to see if you are at a higher risk for serious skin reactions with this medicine. Symptoms may include:**
    - skin rash
    - hives
    - sores in your mouth
    - blistering or peeling of the skin
2. **Carbamazepine Extended-Release Capsules may cause rare but serious blood problems. Symptoms may include:**
    - fever, sore throat or other infections that come and go or do not go away
    - easy bruising
    - red or purple spots on your body
    - bleeding gums or nose bleeds
    - severe fatigue or weakness
3. **Like other antiepileptic drugs, Carbamazepine Extended-Release Capsules may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

    Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
    - thoughts about suicide or dying
    - attempt to commit suicide
    - new or worse depression
    - new or worse anxiety
    - feeling agitated or restless
    - panic attacks
    - trouble sleeping (insomnia)
    - new or worse irritability
    - acting aggressive, being angry, or violent
    - acting on dangerous impulses
    - an extreme increase in activity and talking (mania)
    - other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop Carbamazepine Extended-Release Capsules without first talking to a healthcare provider.

Stopping Carbamazepine Extended-Release Capsules suddenly can cause serious problems.

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

What is Carbamazepine Extended-Release Capsules?

Carbamazepine Extended-Release Capsules is a medicine used to treat:

- certain types of seizures (partial, tonic-clonic, mixed)
- certain types of nerve pain (trigeminal and glossopharyngeal neuralgia).

Carbamazepine Extended-Release Capsules is not a regular pain medicine and should not be used for aches or pains.

Who should not take Carbamazepine Extended-Release Capsules?

Do not take Carbamazepine Extended-Release Capsules if you:

- have a history of bone marrow depression
- are allergic to carbamazepine or any of the ingredients in Carbamazepine Extended-Release Capsules. See the end of this Medication Guide for a complete list of ingredients in Carbamazepine Extended-Release Capsules.
- take nefazodone
- are allergic to antidepressant medications called tricyclic (TCAs).
- have taken a medicine called Monoamine Oxidase Inhibitor (MAOI) in the last 14 days.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

What should I tell my healthcare provider before taking Carbamazepine Extended-Release Capsules?

Before you take Carbamazepine Extended-Release Capsules, tell your healthcare provider if you:

- have or ever had heart problems
- have or ever had blood problems
- have or ever had liver or kidney problems
- have or ever had allergic reactions to medicines
- have or ever had increased pressure in your eye
- have or have had suicidal thoughts or actions, depression or mood problems
- have any other medical conditions
- drink grapefruit juice or eat grapefruit
- use birth control. Carbamazepine Extended-Release Capsules may make your birth control less effective. Tell your healthcare provider if your menstrual bleeding changes while you take birth control and Carbamazepine Extended-Release Capsules.
- are pregnant or plan to become pregnant. Carbamazepine Extended-Release Capsules may harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking Carbamazepine Extended-Release Capsules. You and your healthcare provider should decide if you should take Carbamazepine Extended-Release Capsules while you are pregnant.
    - If you become pregnant while taking Carbamazepine Extended-Release Capsules, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy. You can enroll in this registry by calling 1-888-233-2334.
- are breastfeeding or plan to breastfeed. Carbamazepine Extended-Release Capsules passes into breast milk. You and your healthcare provider should discuss whether you should take Carbamazepine Extended-Release Capsules or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Taking Carbamazepine Extended-Release Capsules with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take Carbamazepine Extended-Release Capsules?

- Take Carbamazepine Extended-Release Capsules exactly as prescribed. Your doctor will tell you how much Carbamazepine Extended-Release Capsules to take.
- Your healthcare provider may change your dose. Do not change your dose of Carbamazepine Extended-Release Capsules without talking to your healthcare provider.
- Do not stop taking Carbamazepine Extended-Release Capsules without first talking to your healthcare provider. Stopping Carbamazepine Extended-Release Capsules suddenly can cause serious problems. Stopping seizure medicine suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).
- Take Carbamazepine Extended-Release Capsules with or without food.
- **Do not crush, chew, or break** Carbamazepine Extended-Release Capsules or the beads inside of the capsules. But, Carbamazepine Extended-Release Capsules can be opened and sprinkled over food such as a teaspoon of applesauce. Tell your healthcare provider if you can not swallow Carbamazepine Extended-Release Capsules whole.
- If you take too much Carbamazepine Extended-Release Capsules, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking Carbamazepine Extended-Release Capsules?

- Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking Carbamazepine Extended-Release Capsules until you talk to your healthcare provider. Carbamazepine Extended-Release Capsules taken with alcohol or drugs may make your sleepiness or dizziness worse.
- Do not drive, or operate heavy machinery, or do other dangerous activities until you know how Carbamazepine Extended-Release Capsules affects you. Carbamazepine Extended-Release Capsules can slow your thinking and motor skills.

What are the possible side effects of Carbamazepine Extended-Release Capsules?

See **"What is the most important information I should know about Carbamazepine Extended-Release Capsules?"**

Carbamazepine Extended-Release Capsules may cause other serious side effects including:

- Irregular heartbeat - symptoms include:
  - Fast, slow, or pounding heartbeat
  - Shortness of breath
  - Feeling lightheaded
  - Fainting
- Liver problems - symptoms include:
  - yellowing of your skin or the whites of your eyes
  - dark urine
  - pain on the right side of your stomach area (abdominal pain)
  - easy bruising
  - loss of appetite
  - nausea or vomiting

Get medical help right away if you have any of the symptoms listed above or listed in

"What is the most important information I should know about Carbamazepine Extended-Release Capsules".

The most common side effects of Carbamazepine Extended-Release Capsules include:

- dizziness
- drowsiness
- problems with walking and coordination (unsteadiness)
- nausea
- vomiting

These are not all the side effects of Carbamazepine Extended-Release Capsules. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Carbamazepine Extended-Release Capsules?

- Store Carbamazepine Extended-Release Capsules between 59°F to 86°F (15°C to 30°C).
- Keep Carbamazepine Extended-Release Capsules out of the light.
- Keep Carbamazepine Extended-Release Capsules capsules dry.

Keep Carbamazepine Extended-Release Capsules and all medicines out of the reach of children.

General information about Carbamazepine Extended-Release Capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Carbamazepine Extended-Release Capsules for a condition for which it was not prescribed. Do not give Carbamazepine Extended-Release Capsules to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Carbamazepine Extended-Release Capsules. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Carbamazepine Extended-Release Capsules that is written for health professionals.

What are the ingredients in Carbamazepine Extended-Release Capsules?

Active ingredient: carbamazepine

Inactive ingredients: silicified microcrystalline cellulose, oleic acid, ethylcellulose, medium chain triglycerides, polyethylene glycols, hypromellose and sodium lauryl sulfate.

In addition:

- the 300 mg capsule shell contains gelatin, D&C Red #28, FD&C Blue #1, black iron oxide, titanium dioxide and are imprinted with black ink.

The imprinting ink contains the following: black iron oxide, D&C Yellow # 10 Aluminum Lake, FD&C Blue #1/ Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/ Indigo Carmine Aluminum Lake, FD&C Red # 40/ Allura Red AC Aluminum Lake, propylene glycol and shellac glaze.

This Medication Guide has been approved by the US Food and Drug Administration.

Manufactured by:
Nostrum Laboratories Inc.
1800 N. Topping Avenue
Kansas City, MO 64120

Rev: April 2011

ANDA 076697
Carbamazepine Extended-Release Capsules

Antiepileptic Drug Class

Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to inform patients about the serious risks associated with the use of Carbamazepine Extended-Release Capsules.

II. REMS ELEMENTS

A. Medication Guide

Nostrum Laboratories, Inc. will ensure that a currently approved Medication Guide is dispensed with each Carbamazepine Extended-Release Capsules prescription in accordance with 21 CFR 208.24. Carbamazepine Extended-Release Capsules is an extended-release formulation for twice daily administration and available in 100 mg, 200 mg, and 300 mg two-piece hard gelatin capsules supplied in bottles of 120 capsules. Nostrum Laboratories, Inc. sells Carbamazepine Extended-Release Capsules only to wholesalers and distributors and does not sell the product directly to dispensing pharmacies or pharmacy chains.

In accordance with 21 CFR 208.24(d), Nostrum Laboratories, Inc. will include a statement on the Carbamazepine Extended-Release Capsules container labels to alert the authorized dispensers to dispense the Medication Guide with the product. The statement will be as follows: Dispense the accompanying Medication Guide to each patient.

A minimum of 2 Medication Guides will be provided with a bottle of 120 capsules for a product where the usual or average dose is 2 capsules daily and a monthly supply is thus 60 capsules.

The Medication Guide will also be made available on the Nostrum Laboratories, Inc. web site at (www.nostrumlabs.com).

B. Timetable for Submission of Assessments

Not applicable for ANDA applications.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-697

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-697

Date of Submission: May 20, 2003

Applicant's Name: Nostrum Pharmaceuticals, Inc.

Established Name: Carbamazepine Extended-release Capsules, 300 mg

Labeling Deficiencies:

1. CONTAINER – 30s and 120s

   a. Because your stability studies were performed at 25 ± 2 ° C/60% ± 5%RH revise your storage temperature recommendation to read: Store at 20-25° C (68-77° F) [See USP Controlled Room Temperature].

   b. Please note that this drug product is not the subject of a USP monograph, therefore delete "USP" in association with the established name.

2. INSERT

   a. GENERAL

      (1) See comment 1b under CONTAINER.

      (2) Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

   b. DESCRIPTION

      (1) Replace "hydroxypropyl methycellulose" with "hypromellose".

      (2) Your components and composition statements includes gelatin as a capsule component, however, gelatin is not included in the inactive ingredients in your DESCRIPTION section. Please revise or comment.

   c. CLINICAL PHARMACOLOGY

      Pharmacokinetics, first paragraph, second sentence, change "(b) (4)" to "200 mg".

   d. HOW SUPPLIED

      See comment 1a under container.

Please revise your labels and labeling, as instructed above, and submit in final printed labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Carbatrol® Capsules
NDA Number: 20-712
NDA Drug Name: Carbatrol ® (carbamazepine) Extended-release capsules
NDA Firm: Shire Pharmaceuticals
Date of Approval of NDA Insert and supplement #: 1-12-98 (acknowledged and retained)
Has this been verified by the MIS system for the NDA? No, information obtained from project manager
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Labels submitted for side-by-side review.

5912013	June 15, 2016	U-277	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	IV	**Same as**

Exclusivity Data– NDA 20-712

Code	Reference	Expiration	Labeling Impact
	There are no unexpired exclusivities for this drug product		

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - NDA: Store at 15 - 25°C (59 -77°F)
   - ANDA: Store at (b) (4)

   Firm has been asked to revise to: Store at 20-25° C (68-77° F) [See USP Controlled Room Temperature].

5. DISPENSING STATEMENT COMPARISON
   - NDA: Dispense in a tight light-resistant container as defined by the USP.
   - ANDA: Dispense in a tight light-resistant container as defined by the USP.

6. PACKAGE CONFIGURATION
   - NDA: 120's
   - ANDA: 30's, 120's

7. CONTAINER/CLOSURE -Vol. B1.3, pg.1175
   - Container: HDPE
   - Closure: CRC

8. FINISHED DOSAGE FORM
   - ANDA: Hard gelatin capsule, purple opaque body with purple opaque cap printed with the (b) (4) logo in black ink.

9. Martec Scientific is the manufacturer for this drug product. (Vol B 1.2, pg.544)

Date of Review: October 21, 2003 Date of Submission: May 20, 2003

Primary Reviewer: Michelle Dillahunt Date: 10/29/03

Team Leader: Lillie Golson Date: 10/29/03

cc:

ANDA:76-697
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-697

Date of Submission: January 19, 2004

Applicant's Name: Nostrum Pharmaceuticals, Inc.

Established Name: Carbamazepine Extended-release Capsules, 300 mg

Labeling Deficiencies:

1. CONTAINER – 30s and 120s

   Revise your storage temperature recommendation to read: Store at 20-25° C (68-77° F) [See USP Controlled RoomTemperature].

2. INSERT

   a. GENERAL

      (1) When expressing "µg", use "mcg" throughout your insert.

      (2) Use the term "to" rather than a hyphen when expressing a range.

   b. DOSAGE AND ADMINISTRATION

      Upon further review, please make the following changes;

      (1) Epilepsy -Adults and children over 12 years of age. Initial., revise to "200 mg twice daily. Increase at weekly intervals by adding up to 200 mg/day until optimal....."

      (2) Trigeminal Neuralgia, Initial, first sentence, revise to read; "On the first day, start with one 200 mg capsule. This daily dose may be increased by up to 200 mg/day every 12 hours....."

      (3) Trigeminal Neuralgia, Initial, penultimate sentence, revise to read; "However, some patients may be maintained on as little as 200 mg daily, while.....

   c. HOW SUPPLIED

      See comment 1 under container.

Please revise your labels and labeling, as instructed above, and submit in final printed labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Carbatrol® Capsules
NDA Number: 20-712
NDA Drug Name: Carbatrol ® (carbamazepine) Extended-release capsules
NDA Firm: Shire Pharmaceuticals
Date of Approval of NDA Insert and supplement #: approved 9/30/97/1-12-98 (acknowledged and retained)
Has this been verified by the MIS system for the NDA? No, information obtained from project manager
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Labels submitted for side-by-side review.

labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?	x		
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES TO CHEMIST:

1. The 300 mg capsule contains iron oxides. According to 21 CFR 73.1200, the total daily dose of elemental iron should not exceed 5 mg. Is the amount of daily elemental iron within regulations if an adult patient were to take the maximum recommended daily dose, 1600 mg?

The chemist has addressed this to the firm in a chemistry deficiency.

FOR THE RECORD:

1. MODEL LABELING – Carbatrol ® (carbamazepine) Extended-release capsules, approved 9/30/97/ acknowledged and retained on 1/12/98.

2. INACTIVE INGREDIENTS
   Consistent with the inactive ingredients listed on page 255, Vol.B1.1.

3. PATENTS/EXCLUSIVITIES
   Patent Data – NDA 20-712

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert			x

5326570	July 5, 2011	U-215	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	IV	**Same as**
5912013	June 15, 2016	U-277	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	IV	**Same as**

Exclusivity Data– NDA 20-712

Code	Reference	Expiration	Labeling Impact
	There are no unexpired exclusivities for this drug product		

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - NDA: Store at 15 - 25^{0}C (59 -77^{0}F)
   - ANDA: Store at 20 - 25^{0}C (68 -77^{0}F)

   Firm has been asked to revise to: Store at 20-25° C (68-77° F) [See USP Controlled Room Temperature].

5. DISPENSING STATEMENT COMPARISON
   - NDA: Dispense in a tight light-resistant container as defined by the USP.
   - ANDA: Dispense in a tight light-resistant container as defined by the USP.

6. PACKAGE CONFIGURATION
   - NDA: 120's
   - ANDA: 30's, 120's

7. CONTAINER/CLOSURE -Vol. B1.3, pg.1175
   - Container: HDPE
   - Closure: CRC

8. FINISHED DOSAGE FORM
   - ANDA: Hard gelatin capsule, purple opaque body with purple opaque cap printed with the (b) (4) logo in black ink.

9. Martec Scientific is the manufacturer for this drug product. (Vol B 1.2, pg.544)

Date of Review: January 23, 2004 Date of Submission: January 19, 2004

Primary Reviewer: Michelle Dillahunt Date: 2/4/04

Team Leader: Lillie Golson Date: 2/4/04

cc:

ANDA:76-697
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
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Review

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-697

Date of Submission: February 23, 2004

Applicant's Name: Nostrum Pharmaceuticals, Inc.

Established Name: Carbamazepine Extended-release Capsules, 300 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER – 30s and 120s
Satisfactory in FPL as of the February 23, 2004 submission.

INSERT
Satisfactory in FPL as of the February 23, 2004 submission.(Vol 5.1;Revised February 2004)

Revisions needed pre-approval:
The firm provided a commitment on 3/24/04 to make the following revision prior to approval.
INSERT
DOSAGE AND ADMINISTRATION, Epilepsy, third sentence; change "1200 daily" to "1200 mg daily"

BASIS OF APPROVAL:
Patent Data – NDA 20-712

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5326570	July 5, 2011	U-215	TREATMENT OF EPILEPSY TWICE DAILY. TREATING A PATIENT BY ADMINISTERING CARBAMAZEPINE IN A DOSAGE FORM CAPABLE OF MAINTAINING BLOOD CONCENTRATION FROM 4-12MCG/ML OVER 12 HOURS	IV	Same as
5912013	June 15, 2016	U-277	NEUROLOGICAL AND OTHER DISORDERS (TREATMENT OF EPILEPSY, BID ORAL DOSING)	IV	Same as

Exclusivity Data– NDA 20-712

Code	Reference	Expiration	Labeling Impact
	There are no unexpired exclusivities for this drug product		

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Carbatrol® Capsules
NDA Number: 20-712
NDA Drug Name: Carbatrol ® (carbamazepine) Extended-release capsules
NDA Firm: Shire Pharmaceuticals
Date of Approval of NDA Insert and supplement #: approved 9/30/97/1-12-98 (acknowledged and retained)
Has this been verified by the MIS system for the NDA? No, information obtained from project manager
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels:
Labels submitted for side-by-side review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	

Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?	x		
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES TO CHEMIST:

1. The 300 mg capsule contains iron oxides. According to 21 CFR 73.1200, the total daily dose of elemental iron should not exceed 5 mg. Is the amount of daily elemental iron within regulations if an adult patient were to take the maximum recommended daily dose, 1600 mg?

From chemistry review #2 (Damaris Maldonado)

"The maximum number of capsules recommended per day is two at start of therapy; however, doses up to 1600 mg may be possible, (see package insert-Dosage and Administration section) which computes to a maximum of daily dose of elemental iron of (b) (4) mg, which is less than the MDA of 5 mg."

FOR THE RECORD:

1. MODEL LABELING – Carbatrol ® (carbamazepine) Extended-release capsules,NDA 20-712 approved 9/30/97 acknowledged and retained on 1/12/98.

2. The firm currently only has an application for the 300 mg capsule. The DOSAGE AND ADMINISTRATION Section, recommends a starting dose of 200 mg twice daily. Increase at weekly intervals by adding up to 200 mg/day until optimal response is obtained. The firm will not be able to use their 300 mg capsule for the initial dosage or for increasing the dose at weekly intervals. I spoke to Mr. Paul Sudhakar who informed me that they are working on the chemistry for the 200 mg capsule.

3. INACTIVE INGREDIENTS
   Consistent with the inactive ingredients listed on page 255, Vol.B1.1.

4. PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-712

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5326570	July 5, 2011	U-215	TREATMENT OF EPILEPSY TWICE DAILY. TREATING A PATIENT BY ADMINISTERING CARBAMAZEPINE IN A DOSAGE FORM CAPABLE OF MAINTAINING BLOOD CONCENTRATION FROM 4-12MCG/ML OVER 12 HOURS	IV	Same as
5912013	June 15, 2016	U-277	NEUROLOGICAL AND OTHER DISORDERS (TREATMENT OF EPILEPSY, BID ORAL DOSING)	IV	Same as

Exclusivity Data– NDA 20-712

Code	Reference	Expiration	Labeling Impact
	There are no unexpired exclusivities for this drug product		

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - NDA: Store at 15 - 25^{0}C (59 -77^{0}F)
   - ANDA: Store at 20-25° C (68-77° F) [See USP Controlled Room Temperature].

6. DISPENSING STATEMENT COMPARISON
   - NDA: Dispense in a tight light-resistant container as defined by the USP.
   - ANDA: Dispense in a tight light-resistant container as defined by the USP.

7. PACKAGE CONFIGURATION
   - NDA: 120's
   - ANDA: 30's, 120's

8. CONTAINER/CLOSURE -Vol. B1.3, pg.1175
   - Container: HDPE
   - Closure: CRC

9. FINISHED DOSAGE FORM
   - ANDA: Hard gelatin capsule, purple opaque body with purple opaque cap printed with the (b) (4) logo in black ink.

10. Martec Scientific is the manufacturer for this drug product. (Vol B 1.2, pg.544)
Nostrum Pharmaceuticals is the ANDA sponsor and the ANDA owner and is responsible for the fiduciary, legal and product commercialization activities.
(b) (4) is the distributor of the product.

Date of Review: March 12, 2004 Date of Submission: February 23, 2004

Primary Reviewer: Michelle Dillahunt Date: 3/24/04

Team Leader: Lillie Golson Date: 3/24/04

cc:

ANDA:76-697
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\NOSTRUM\LTRS&REV\76697ap.L.doc
Review

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-697

Dates of Submissions: April 28, 2008 & September 25, 2008

Applicant's Name: Nostrum Pharmaceuticals, Inc.

Established Name: Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg

Proposed Proprietary Name: None

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? E-submission

CONTAINER – 30s and 120s for 100 mg, 200 mg, and 300 mg.

- Satisfactory in final print as of April 28, 2008 submission.

PROFESSIONAL INSERT:

- Satisfactory in final print as of September 25, 2008 submission.

REVISIONS NEEDED POST-APPROVAL: Yes

- Revise the storage temperature recommendation as follows:

  "Store at 20°-25° (68° – 77°F);excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]"

NOTE TO CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING – Carbatrol ® (carbamazepine) Extended-release capsules (20-712/S-029), approved December 11, 2007.

2. INACTIVE INGREDIENTS

   Consistent with the inactive ingredients listed on page 255, Vol.B1.1**.**

3. PATENTS/EXCLUSIVITIES

   Patent Data – NDA 20-712

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5326570	July 5, 2011	U-215	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	**IV**	**Same as**

5912013	June 15, 2016	U-277	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	**IV**	**Same as**

Exclusivity Data– NDA 20-712

- There is no unexpired exclusivity for this drug product.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   - NDA: Store at 15 - 25^{0}C (59 -77^{0}F)

   - ANDA: Store at controlled room temperature 20 - 25^{0}C (68 -77^{0}F)

5. DISPENSING STATEMENT COMPARISON
   - NDA: Dispense in a tight light-resistant container as defined by the USP.
   - ANDA: Dispense in a tight light-resistant container as defined by the USP.

6. PACKAGE CONFIGURATION
   - NDA: 120's
   - ANDA: 30's, 120's

7. CONTAINER/CLOSURE -Vol. B1.3, pg.1175
   - Container: HDPE
   - Closure: CRC

8. FINISHED DOSAGE FORM

   - 100 mg - Hard gelatin capsule (dark green opaque body with dark green opaque cap) printed with the "NC" / "100" logo in black ink.
   - 200 mg - Hard gelatin capsule (yellow opaque body with yellow opaque cap) printed with the "NC" / "200" logo in black ink.
   - 300 mg - Hard gelatin capsule (purple opaque body with purple opaque cap) printed with the "NC" / "300" logo in black ink.

9. Manufactured and Distributed by:

   Nostrum Laboratories, Inc.
   Kansas City, MO 64120

Date of Review: October 15, 2008 Date of Submission: April 28, 2008 & September 25, 2008

Primary Reviewer: _____ _____
Melaine Shin Date:

Team Leader: _____ _____
Lillie Golson Date:

cc: ANDA 76-697
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
Review
M:\LABELING REVIEWS\ANDA 76-697 Carbamazepine (Nostrum)\76697 AP1. labeling.doc
FINAL: October 15, 2008

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

/s/

Melaine Shin
10/15/2008 11:27:47 PM
LABELING REVIEWER

Lillie Golson
10/15/2008 11:30:37 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-697

Dates of Submissions: May 25, 2009

Applicant's Name: Nostrum Pharmaceuticals, Inc.

Established Name: Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg

Proposed Proprietary Name: None

LABELING DEFICIENCIES:

GENERAL:

- Revise the storage temperature recommendation as follows:

  "Store at 20°-25° (68° – 77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]"

CONTAINER – 30s and 120s for 100 mg, 200 mg, and 300 mg.

- See comment under GENERAL.

PROFESSIONAL INSERT:

- Please note that the only 300 mg strength is eligible for full approval. In order to approve the 300 mg strength, we ask that you remove reference to 100 mg and 200 mg strengths from your insert labeling.

- See comment under GENERAL.

Please revise your labeling, as instructed above, and submit electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FOR THE RECORD:

Note: Please below email discussing a split full approval on the 300 mg and TA on the 100 mg and 200 mg.

From: Shimer, Martin
Sent: Tuesday, May 26, 2009 2:43 PM
To: Kwok, Lisa; Shin, Melaine M
Cc: Rickman, William P; West, Robert L
Subject: Approval for ANDA 76-697

Lisa and Melaine,

This e-mail is to let you both know that the subject ANDA will be eligible for a split Full approval on the 300 mg strength and TA on the 100 mg and 200 mg strengths. Nostrum has informed OGD that they were sued on two separate occassions. The first suit was in 2003, with this suit covering the 300 mg strength. The second suit was filed in 2008, with respect to the 100 mg and 200 mg strengths. Nostrum has stated that both cases remain pending with no decision having been rendered by the court. Since the 30 month stay has long since expired on the 300 mg strength this strength will be eligible for Full Approval. The 30 month stay on the 100 mg and 200 mg strengths will not end until 11/19/2010 so these two strengths are eligible for TA only.

The applicant will need to be notified to revise their labeling to remove reference to the 100 mg and 200 mg strengths so that we can move forward with Fully Approving the 300 mg strength.

Thanks,

Marty

---

1. MODEL LABELING – Carbatrol ® (carbamazepine) Extended-release capsules (20-712/S-029), approved December 11, 2007.

2. INACTIVE INGREDIENTS

   Consistent with the inactive ingredients listed on page 255, Vol.B1.1**.**

3. PATENTS/EXCLUSIVITIES

   Patent Data – NDA 20-712

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5326570	July 5, 2011	U-215	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	**IV**	**Same as**
5912013	June 15, 2016	U-277	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	**IV**	**Same as**

Exclusivity Data– NDA 20-712

- There is no unexpired exclusivity for this drug product.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- NDA: Store at 15 - 25^{0}C (59 -77^{0}F)

- ANDA: Store at controlled room temperature 20 - 25^{0}C (68 -77^{0}F)

**I asked the firm to revise as follows:

"Store at 20°-25° (68° – 77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]"

5. DISPENSING STATEMENT COMPARISON
   - NDA: Dispense in a tight light-resistant container as defined by the USP.
   - ANDA: Dispense in a tight light-resistant container as defined by the USP.

6. PACKAGE CONFIGURATION
   - NDA: 120's
   - ANDA: 30's, 120's

7. CONTAINER/CLOSURE -Vol. B1.3, pg.1175
   - Container: HDPE
   - Closure: CRC

8. FINISHED DOSAGE FORM

- 100 mg - Hard gelatin capsule (dark green opaque body with dark green opaque cap) printed with the "NC" / "100" logo in black ink.
- 200 mg - Hard gelatin capsule (yellow opaque body with yellow opaque cap) printed with the "NC" / "200" logo in black ink.
- 300 mg - Hard gelatin capsule (purple opaque body with purple opaque cap) printed with the "NC" / "300" logo in black ink.

9. Manufactured and Distributed by:

   Nostrum Laboratories, Inc.
   Kansas City, MO 64120

Date of Review: May 27, 2009 Date of Submission: May 25, 2009

Primary Reviewer: _____ _____
Melaine Shin Date:

Team Leader: _____ _____
Lillie Golson Date:

cc: ANDA 76-697
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
Review
M:\LABELING REVIEWS\ANDA 76-697 Carbamazepine (Nostrum)\76697 NA. labeling.doc
FINAL: May 27, 2009

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

/s/

Melaine Shin
5/29/2009 04:20:20 PM
LABELING REVIEWER

Lillie Golson
5/29/2009 04:23:27 PM
LABELING REVIEWER

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-697

Dates of Submissions: June 10, 2009

Applicant's Name: Nostrum Pharmaceuticals, Inc.

Established Name: Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg

Proposed Proprietary Name: None

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? E-submission

CONTAINER – 30s and 120s for 100 mg, 200 mg, and 300 mg.

- Satisfactory in final print as of June 10, 2009 submission.

PROFESSIONAL INSERT:

- Satisfactory in final print as of May 25, 2009 submission – 100 mg, 200 mg, and 300 mg
- Satisfactory in final print as of June 10, 2009 submission – 300 mg

REVISIONS NEEDED POST-APPROVAL: Yes

- The firm will decrease the prominence of the company logo to make the established name and strength the most prominent on the labels.

- Revise the storage temperature recommendation as follows for the combined insert labeling:

  "Store at 20°-25° (68° – 77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]"

NOTE TO CHEMIST: None

FOR THE RECORD:

**The firm submitted the insert labeling for the 300 mg strength.

Note: Please below email discussing a split full approval on the 300 mg and TA on the 100 mg and 200 mg.

From: Shimer, Martin
Sent: Tuesday, May 26, 2009 2:43 PM
To: Kwok, Lisa; Shin, Melaine M
Cc: Rickman, William P; West, Robert L
Subject: Approval for ANDA 76-697

Lisa and Melaine,

This e-mail is to let you both know that the subject ANDA will be eligible for a split Full approval on the 300 mg strength and TA on the 100 mg and 200 mg strengths. Nostrum has informed OGD that they were sued on two separate occassions. The first suit was in 2003, with this suit covering the 300 mg strength.

The second suit was filed in 2008, with respect to the 100 mg and 200 mg strengths. Nostrum has stated that both cases remain pending with no decision having been rendered by the court. Since the 30 month stay has long since expired on the 300 mg strength this strength will be eligible for Full Approval. The 30 month stay on the 100 mg and 200 mg strengths will not end until 11/19/2010 so these two strengths are eligible for TA only.

The applicant will need to be notified to revise their labeling to remove reference to the 100 mg and 200 mg strengths so that we can move forward with Fully Approving the 300 mg strength.

Thanks,

Marty

---

1. MODEL LABELING – Carbatrol ® (carbamazepine) Extended-release capsules (20-712/S-030), approved April 23, 2009.

2. INACTIVE INGREDIENTS

   Consistent with the inactive ingredients listed on page 255, Vol.B1.1**.**

3. PATENTS/EXCLUSIVITIES

   Patent Data – NDA 20-712

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5326570	July 5, 2011	U-215	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	**IV**	**Same as**
5912013	June 15, 2016	U-277	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	**IV**	**Same as**

Exclusivity Data– NDA 20-712

- There is no unexpired exclusivity for this drug product.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   NDA: Store at 15 - 25^0C (59 -77^0F)

   ANDA: Store at 20°-25° (68° – 77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]"

5. DISPENSING STATEMENT COMPARISON

   - NDA: Dispense in a tight light-resistant container as defined by the USP.
   - ANDA: Dispense in a tight light-resistant container as defined by the USP.

6. PACKAGE CONFIGURATION
   - NDA: 120's
   - ANDA: 30's, 120's

7. CONTAINER/CLOSURE -Vol. B1.3, pg.1175

- Container: HDPE
- Closure: CRC

8. FINISHED DOSAGE FORM

- 100 mg - Hard gelatin capsule (dark green opaque body with dark green opaque cap) printed with the “NC” / “100” logo in black ink.
- 200 mg - Hard gelatin capsule (yellow opaque body with yellow opaque cap) printed with the “NC” / “200” logo in black ink.
- 300 mg - Hard gelatin capsule (purple opaque body with purple opaque cap) printed with the “NC” / “300” logo in black ink.

9. Manufactured and Distributed by:

Nostrum Laboratories, Inc.
Kansas City, MO 64120

Date of Review: June 16, 2009 Date of Submission: June 10, 2009

Primary Reviewer: _____ _____
Melaine Shin Date:

Team Leader: _____ _____
Lillie Golson Date:

cc: ANDA 76-697
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
Review
M:\LABELING REVIEWS\ANDA 76-697 Carbamazepine (Nostrum)\76697 AP2. labeling.doc
FINAL: June 25, 2009

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

/s/

Melaine Shin
6/25/2009 01:00:12 PM
LABELING REVIEWER

Lillie Golson
6/25/2009 01:51:28 PM
LABELING REVIEWER

APPROVAL SUMMARY #3
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-697

Dates of Submissions: September 29, 2009 & October 6, 2009

Applicant's Name: Nostrum Pharmaceuticals, Inc.

Established Name: Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg

Proposed Proprietary Name: None

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? E-submission

CONTAINER – 30s and 120s for 100 mg, 200 mg, and 300 mg.

- Satisfactory in final print as of June 10, 2009 submission.

PROFESSIONAL INSERT:

- Satisfactory in final print as of September 29, 2009 submission – 300 mg
- Satisfactory in final print as of October 6, 2009 submission – 100 mg & 200 mg

REVISIONS NEEDED POST-APPROVAL: Yes

- The firm will decrease the prominence of the company logo to make the established name and strength the most prominent on the labels.

NOTE TO CHEMIST: None

FOR THE RECORD:

**The firm submitted the insert labeling for the 300 mg strength.

Note: Please below email discussing a split full approval on the 300 mg and TA on the 100 mg and 200 mg.

From: Shimer, Martin
Sent: Tuesday, May 26, 2009 2:43 PM
To: Kwok, Lisa; Shin, Melaine M
Cc: Rickman, William P; West, Robert L
Subject: Approval for ANDA 76-697

Lisa and Melaine,

This e-mail is to let you both know that the subject ANDA will be eligible for a split Full approval on the 300 mg strength and TA on the 100 mg and 200 mg strengths. Nostrum has informed OGD that they were sued on two separate occassions. The first suit was in 2003, with this suit covering the 300 mg strength. The second suit was filed in 2008, with respect to the 100 mg and 200 mg strengths. Nostrum has stated

that both cases remain pending with no decision having been rendered by the court. Since the 30 month stay has long since expired on the 300 mg strength this strength will be eligible for Full Approval. The 30 month stay on the 100 mg and 200 mg strengths will not end until 11/19/2010 so these two strengths are eligible for TA only.

The applicant will need to be notified to revise their labeling to remove reference to the 100 mg and 200 mg strengths so that we can move forward with Fully Approving the 300 mg strength.

Thanks,

Marty

**It is to note that based on the email communication between the Bio reviewer and Labeling Branch as attached below, the firm revised the Food Effect section of their labeling.

1. MODEL LABELING – Carbatrol ® (carbamazepine) Extended-release capsules (20-712/S-030), approved April 23, 2009.

2. INACTIVE INGREDIENTS

   Consistent with the inactive ingredients listed on page 255, Vol.B1.1**.**

3. PATENTS/EXCLUSIVITIES

   Patent Data – NDA 20-712

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5326570	July 5, 2011	U-215	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	**IV**	**None**
5912013	June 15, 2016	U-277	Advanced drug delivery system and method of treating psychiatric, neurological and other disorders with carbamazepine	**IV**	**None**

Exclusivity Data– NDA 20-712

- There is no unexpired exclusivity for this drug product.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   NDA: Store at 15 - 25^{0}C (59 -77^{0}F)

   ANDA: Store at 20°-25° (68° – 77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]"

5. DISPENSING STATEMENT COMPARISON

   - NDA: Dispense in a tight light-resistant container as defined by the USP.
   - ANDA: Dispense in a tight light-resistant container as defined by the USP.

6. PACKAGE CONFIGURATION
   - NDA: 120's

- ANDA: 30's, 120's

7. CONTAINER/CLOSURE -Vol. B1.3, pg.1175

   - Container: HDPE
   - Closure: CRC

8. FINISHED DOSAGE FORM

- 100 mg - Hard gelatin capsule (dark green opaque body with dark green opaque cap) printed with the "NC" / "100" logo in black ink.
- 200 mg - Hard gelatin capsule (yellow opaque body with yellow opaque cap) printed with the "NC" / "200" logo in black ink.
- 300 mg - Hard gelatin capsule (purple opaque body with purple opaque cap) printed with the "NC" / "300" logo in black ink.

9. Manufactured and Distributed by:

   Nostrum Laboratories, Inc.
   Kansas City, MO 64120

From: Golson, Lillie D
Sent: Monday, September 28, 2009 4:34 PM
To: Shin, Melaine M
Cc: Golson, Lillie D
Subject: FW: ANDA 76-697

Bio agrees with the recommendation to simply carve out that paragraph in the labeling. So, go ahead and complete your review.

Thanks

From: Raines, Kimberly
Sent: Monday, September 28, 2009 4:21 PM
To: Golson, Lillie D
Cc: Davit, Barbara M; Dhariwal, Kuldeep R; Chaurasia, Chandra S
Subject: RE: ANDA 76-697

Hi Lillie,

This labeling issue was discussed with the DBE2 management (please see minutes below) on September 8, 2009. The summarizing question was, *How will the sameness in terms of labeling between RLD and generic drug be interpreted?* From the revised labeling provided below (9/28/2009), I believe the sameness between the RLD and generic product are intact. We are in concurrence with this carve out, as long as, it is within the current guidelines for labeling changes. I hope this answers your question. If you have any additional questions please feel free to ask. Thank you.

Kimberly

From: Golson, Lillie D
Sent: Monday, September 28, 2009 3:25 PM
To: Raines, Kimberly; Chaurasia, Chandra S
Cc: Golson, Lillie D; Shin, Melaine M
Subject: FW: ANDA 76-697

Hi Kimberly,

Upon further consultation, we in labeling have decided that it would be better to carve out the Cmax and Tmax information rather than propose appropriate language. Therefore,
we plan to ask this firm to revise their labeling to use the following for the Food Effect subsection:

Labeling's revised proposal as of 9/28/2009:

Food Effect:
The multiple dose study conducted in the fed state showed that the steady-state Cmax values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

Thank you. We anxiously await your comments regarding this matter.

Lillie

Date of Review: October 20, 2009 Dates of Submissions: September 29, 2009 & October 6, 2009

Primary Reviewer: _____ _____
Melaine Shin Date:

Team Leader: _____ _____
Lillie Golson Date:

cc: ANDA 76-697
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
Review
M:\LABELING REVIEWS\ANDA 76-697 Carbamazepine (Nostrum)\76697 AP3. labeling.doc
FINAL: October 20, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE

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

/s/

MELAINE M SHIN
11/02/2009

LILLIE D GOLSON
11/02/2009

APPROVAL SUMMARY #4

(Supercedes the AP summary for the September 29, 2009 & October 6, 2009 submissions)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76697
Date of Submission:	February 17, 2011, February 24, 2011, March 10, 2011, March 15, 2011, and April 1, 2011
Applicant's Name:	Nostrum Pharmaceuticals, Inc.
Established Name:	Carbamazepine Extended-Release Capsules, 100 mg, 200 mg, and 300 mg

---

LABELING DEFICIENCIES:

1. **CONTAINER:** (Bottles of 30 and 120)
   Satisfactory in FPL as of the February 17, 2011 submission

2. **PROFESSIONAL INSERT:**
   100 mg and 200 mg Strength Only
   300 mg Strength Only
   - 300 mg strength PI is satisfactory in FPL as of the March 15, 2011 submission
   - 100 mg and 200 mg strength PI is satisfactory in FPL as of the March 15, 2011 submission

3. **MEDICATION GUIDE:**
   - 300 mg strength PI is satisfactory in FPL as of the April 1, 2011 submission
   - 100 mg and 200 mg strength PI is satisfactory in FPL as of the April 1, 2011 submission

4. **REMS:**
   Satisfactory as of the February 24, 2011 submission

Post Approval Revisions: Yes

CONTAINER: (Bottles of 30 and 120)

- We encourage you to reduce the font size of the net quantity statement, the company logo, and the “Rx Only” statement. The established name and strength should be the most predominant element of the container label.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Carbatrol
NDA Number: 20712/S-031
NDA Drug Name: Carbatrol (Carbamazepine Extended Release Capsules)
NDA Firm: Shire
Date of Approval of NDA Insert and supplement #: 20712/S-031 by Shire approved January 26, 2011

Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No

NOTE TO THE CHEMIST:

- Do the imprinting inks appearing in the insert differ from those appearing in the application?

From: Patankar, Suhas
Sent: Thursday, March 24, 2011 1:19 PM
To: Stewart, Kendra
Subject: RE: 76697, Carbamazepine Extended-release Capsules

CMC does not have any additional information. Combined information from labeling and CMC is Ok. - Suhas

---

From: Stewart, Kendra
Sent: Thursday, March 24, 2011 1:13 PM
To: Patankar, Suhas
Subject: RE: 76697, Carbamazepine Extended-release Capsules

Does that mean it's okay?

Kendra

From: Patankar, Suhas
Sent: Thursday, March 24, 2011 1:02 PM
To: Stewart, Kendra
Subject: RE: 76697, Carbamazepine Extended-release Capsules

Hi Kendra,

I just received the jackets for the AM. The Vol. B9.5 has (b) (4) CoAs for three sizes (pp. 1763-1769). They all state that Black (b) (4) ink is used for imprinting. However, the composition of ink is not included.

The file you sent from March 14, 2011 Labeling AM does include composition of the two (b) (4) Inks.

Thanks,

Suhas

From: Stewart, Kendra
Sent: Friday, March 18, 2011 11:58 AM
To: Patankar, Suhas
Cc: Stewart, Kendra
Subject: FW: 76697, Carbamazepine Extended-release Capsules

Hi Suhas,

Sorry to bother you again... I had an email discussion with the sponsor on yesterday (see below) and she stated that their imprinting inks have never changed and she forwarded me the attached information. She asserts that what is in the proposed insert is correct. I looked through the attached documents she sent me and I cannot find the imprinting inks as listed in the firm's proposed insert:

Imprinting Ink from Proposed Insert:

The imprinting ink contains the following: black iron oxide, D&C Yellow # 10 Aluminum Lake, FD&C Blue #1/ Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/ Indigo Carmine Aluminum Lake, FD&C Red # 40/ Allura Red AC Aluminum Lake, propylene glycol and shellac glaze.

Perhaps I am missing something.

Is it poss ble that the chemist didn't update the list of ingredients for the imprinting ink when the firm submitted their major amendment in April 2008?

If the firm is in error, I'd l ke to instruct the firm to correct their insert to read x, y, and z but I need definite clarity as to what the list of imprinting inks should read.

Your assistance is greatly appreciated.

Thanks,

Kendra Stewart
Kendra S. Stewart, R.Ph., Pharm.D.
Food and Drug Administration

FOR THE RECORD:

1. MODEL LABELING:
   The reference listed drug for this product is Carbatrol (Carbamazepine Extended Release Capsules) NDA 20712/S-031 by Shire approved January 26, 2011.
   Additional notes:
   - **It is to note that based on the email communication between the Bio reviewer and Labeling Branch as attached below, the firm revised the Food Effect section of their labeling. See FTR#11**
   - There are two inserts… 300 mg strength and 100 mg and 200 mg
     Firm expecting exclusivity for 300 mg strength, therefore submitted separate PIs for the 300 mg and the 100 mg/200 mg strengths

2. MEDWATCH: (Checked on 2/18/2011)
   - In the label
   Information on Carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics) with FDA Alerts

3. PATENT AND EXCLUSIVITY: (Checked on 2/18/2011)

Appl No	Patent No	Patent Expiration	Patent Use Code	Patent Certification	Labeling Impact
N020712	5326570	Jul 5, 2011	**U-215**	**IV**	**None**
N020712	5912013	Jun 15, 2016	**U-277**	**IV**	**None**

U-215 TREATMENT OF EPILEPSY TWICE DAILY. TREATING A PATIENT BY ADMINISTERING CARBAMAZEPINE IN A DOSAGE FORM CAPABLE OF MAINTAINING BLOOD CONCENTRATION FROM 4-12MCG/ML OVER 12 HOURS

U-277 NEUROLOGICAL AND OTHER DISORDERS (TREATMENT OF EPILEPSY, BID ORAL DOSING)

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM: 2.3.P.3
Nostrum Laboratories, Inc.
Kansas City, MO 64120

5. USP: (Checked on 2/18/2011) - none

6. INGREDIENTS: 2.3.P.1
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section 2.3.p.1
- The empty capsule for the 300 mg strength contains iron which computes to a maximum of daily dose of elemental iron of (b) (4) mg, which is less than the MDA of 5 mg. The MDD of the drug product is 1600 mg.

Ink Components:
(b) (4)
Pharmaceutical Glaze (b) (4)
(b) (4) Blaack Iron Oxide
(b) (4)
Propylene Glycol
(b) (4)

Composition of (b) (4):
(b) (4)

Capsule Component:
300 mg strength:
D&C red #28
FD&C blue #1
(b) (4) black iron oxide
Titanium Dioxide
Gelatin

200 mg strength:
D&C Yellow #10
Titanium Dioxide
Gelatin

100 mg strength:
D&C Yellow #10
FD&C blue #1
FD&C Yellow #6
Titanium Dioxide

7. PACKAGING CONFIGURATIONS/PRODUCT LINE:

NDA: 120's
ANDA: 30's, 120's:

8. STORAGE TEMPERATURE STATEMENT COMPARISON – 2.3.P.8
   RLD: Store at 15 - 25^{0}C (59 -77^{0}F)
   ANDA: Store at 20°-25° (68° – 77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]"

9. CONTAINER CLOSURE: 2.3.P.7
   - Container: HDPE:
   - Closure: CRC

10. FINISHED PRODUCT DESCRIPTION:
The product has been accurately described in the How supplied section of the labeling as required by 21 CFR 206, et. al section 2.3.p.5.
   • 100 mg - Hard gelatin capsule (dark green opaque body with dark green opaque cap) printed with the "NC" / "100" logo in black ink.
   • 200 mg - Hard gelatin capsule (yellow opaque body with yellow opaque cap) printed with the "NC" / "200" logo in black ink.
   • 300 mg - Hard gelatin capsule (purple opaque body with purple opaque cap) printed with the "NC" / "300" logo in black ink.

11. FOOD EFFECT SECTION:

From: Golson, Lillie D
Sent: Monday, September 28, 2009 4:34 PM
To: Shin, Melaine M
Cc: Golson, Lillie D
Subject: FW: ANDA 76-697

Bio agrees with the recommendation to simply carve out that paragraph in the labeling. So, go ahead and complete your review.

Thanks

From: Raines, Kimberly
Sent: Monday, September 28, 2009 4:21 PM
To: Golson, Lillie D
Cc: Davit, Barbara M; Dhariwal, Kuldeep R; Chaurasia, Chandra S
Subject: RE: ANDA 76-697

Hi Lillie,

This labeling issue was discussed with the DBE2 management (please see minutes below) on September 8, 2009. The summarizing question was, *How will the sameness in terms of labeling between RLD and generic drug be interpreted?* From the revised labeling provided below (9/28/2009), I believe the sameness between the RLD and generic product are intact. We are in concurrence with this carve out, as long as, it is within the current guidelines for labeling changes. I hope this answers your question. If you have any additional questions please feel free to ask. Thank you.

Kimberly

Hi Kimberly,

Upon further consultation, we in labeling have decided that it would be better to carve out the Cmax and Tmax information rather than propose appropriate language. Therefore,
we plan to ask this firm to revise their labeling to use the following for the Food Effect subsection:

Labeling's revised proposal as of 9/28/2009:

Food Effect:
The multiple dose study conducted in the fed state showed that the steady-state Cmax values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

Thank you. We anxiously await your comments regarding this matter.

Lillie

Date of Review: 2/18/2011 Date of Submission: 2/18/2011

Primary Reviewer: Kendra Stewart

Team Leader: Lillie Golson

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

/s/

KENDRA S STEWART
04/05/2011

LILLIE D GOLSON
04/05/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-697

CHEMISTRY REVIEWS

#1

ANDA 76-697

Carbamazepine Extended Release Capsules, 300 mg

Nostrum Pharmaceuticals, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-697

2. REVIEW #1

3. REVIEW DATE: August 30, 2003

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	20-May-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Nostrum Pharmaceuticals, Inc.
Address:	1800 N. Topping Avenue P.O. Box 33510 Kansas City, MO 64120-3510
Representative:	Paul T. Sudhakar
Telephone:	(816) 241-4144

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Carbamazepine

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Nostrum Pharmaceuticals proposed ANDA for Carbamazepine Extended-release Capsules is the reference listed drug Carbatrol® marketed by Shire Labs. As per the firm's statement, the two existing patents for the RLD will not be infringed by the product listed in this ANDA submission. Carbatrol® is not covered by any exclusivity.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Extended-release Capsules

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

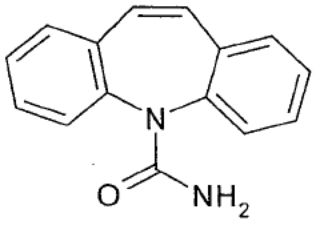
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 5H-dibenz[b,f]azepine-5-carboxamide
Molecular formula: $C_{15}H_{12}N_2O$
Molecular weight: 236.27
Structural Formula:

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)				
	III			4	N/A		(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

17. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Pending		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-697

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The drug product is prescribed as an anticonvulsant. No compendial monograph is available for the Extended-release Capsules. The drug product will be marketed in 30's and 120's packaging sizes. The firm proposes a 24 months expiration dating period.

Drug Substances: Carbamazepine is a white to off white powder, practically insoluble in water and soluble in alcohol and in acetone. The drug substance is a compendial USP item.

Formulation and Manufacturing Process: The drug product is manufactured by (b) (4) and filled in the size 0 opaque purple hard gelatin capsules. The size of the exhibit batch is (b) (4) capsules for the 300 mg strength. Proposed commercial batch size is (b) (4) cpasules.

Method Validation: To be requested for the drug product.

B. Description of How the Drug Product is Intended to be Used

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The firm needs to standardize (b) (4) in the formulation has to be defined. Relationship between Martec and Nostrum to be clarified. Drug substance specifications need

to be revised according to the supplier specifications. The firm needs to specify what tests will be performed by the contract laboratory for post approval batches.

(b) (4)

[redacted]

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-645/DMaldonado/8/30/03

HFD-645/BArnwine/9/25/03

HFD-617/NPark/9/26/03

C. CC Block

ANDA 76-697
ANDA DUP
DIV FILE
Field Copy

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C. Storage Conditions and Labeling Information – For the Labeling Reviewer

The controlled room temperature statement included in the labeling submitted in page 23 (b) (4) of the stability samples from the exhibit batches and the stability protocol.

30. MICROBIOLOGY: N/A

30. SAMPLES AND RESULTS/METHODS VALIDATION STATUS:

32. LABELING:

The labeling review is pending as of this review cycle.

33. ESTABLISHMENT INSPECTION:

Pending; potential OAI alert on Martec Scientific Inc.

34. BIOEQUIVALENCE:

Bio review is pending as of this review cycle.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory

The firm requests a categorical exclusion from the requirement to prepare an Environmental Assessment statement. The drug product will not be administered at a higher dosage level, for a longer duration or for different indications than were previously in effect.

Nostrum certifies that they are in compliance with all federal, state and local laws.

Following this page, 4 pages withheld in full - (b)(4)

37. Please acknowledge that results of stability studies should be reported in annual reports in accordance with 21 CFR 314.81. Also, please revise your post-approval stability commitment to include the first three commercial production lots of the product packaged in the smallest and largest container/closure system in the long term stability program. The same applies to the lots placed in stability on a yearly basis.

Sincerely yours,

Brenda I. Gumucio /for 10/2/03

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-697
DIV FILE
Field Copy

Endorsements:

HFD-645/DMaldonado/8/30/03 DMR 9/29/03.

HFD-645 /BArnwine/9/25/03 BArnwine 10/2/03

HFD-617/NPark/9/26/03 NP 10/8/03

V:\FIRMSNZ\Nostrum\LTRS&REV\76697r1

F/T by: EW 9/29/03

TYPE OF LETTER: NOT APPROVABLE – MINOR

ANDA 76-697

Carbamazepine Extended Release Capsules, 300 mg

Nostrum Pharmaceuticals, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-697

2. REVIEW #2

3. REVIEW DATE: February 19, 2004.

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Original Submission	20-May-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	12-Dec-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Nostrum Pharmaceuticals, Inc.
Address:	1800 N. Topping Avenue P.O. Box 33510 Kansas City, MO 64120-3510
Representative:	Paul T. Sudhakar
Address:	6739 Vahalla Ct Shawnee KS 66217
Telephone:	(816) 507-8249
Fax	913-962-9061

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Carbamazepine

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Nostrum Pharmaceuticals proposed ANDA for Carbamazepine Extended-release Capsules is the reference listed drug Carbatrol® marketed by Shire Labs. As per the firm's statement, the two existing patents for the RLD will not be infringed by the product listed in this ANDA submission. Carbatrol® is not covered by any exclusivity.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Extended-release Capsules

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

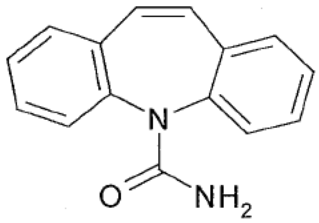
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 5H-dibenz[b,f]azepine-5-carboxamide
Molecular formula: $C_{15}H_{12}N_2O$
Molecular weight: 236.27
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	2/24/04	
	III			4	N/A		(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

17. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	WH	10-27-03	
Methods Validation	Pending		
Labeling	Deficient	2/4/04	
Bioequivalence	Deficient	2/2/04	
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-697

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The drug product is prescribed as an anticonvulsant. No compendial monograph is available for the Extended-release Capsules. The drug product will be marketed in 30's and 120's packaging sizes. The firm proposes a 24 months expiration dating period.

Drug Substances: Carbamazepine is a white to off white powder, practically insoluble in water and soluble in alcohol and in acetone. The drug substance is a compendial USP item.

Formulation and Manufacturing Process: The drug product is manufactured by (b) (4) and filled in the size 0 opaque purple hard gelatin capsules. The size of the exhibit batch is (b) (4) capsules for the 300 mg strength. Proposed commercial batch size is (b) (4) capsules.

B. Description of How the Drug Product is Intended to be Used

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The firm needs to specify what tests will be performed by the contract laboratory for post approval batches. (b) (4) needs to be identified.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-645/DMaldonado/

HFD-645/BArnwine/

HFD-617/NPark/

C. CC Block

ANDA 76-697
ANDA DUP
DIV FILE
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cc: ANDA 76-697
DIV FILE
Field Copy

Endorsements:

HFD-645/DMaldonado/2/19/04 DMR 3/15/04.

HFD-645 /BArnwine/3/5/04 BA (concurred) 3/17/04

HFD-617/NPark/3/9/04 M 3/17/04

V:\FIRMSNZ\Nostrum\LTRS&REV\76697r2

F/T by: EW 3/10/04

TYPE OF LETTER: NOT APPROVABLE – MINOR

#3

ANDA 76-697

Carbamazepine Extended Release Capsules, 300 mg

Nostrum Pharmaceuticals, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-697

2. REVIEW #3

3. REVIEW DATE: March 17, 2005; April 28, 2005; June 22, 2005.

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Original Submission	26-Mar-2003
Amendments	20-May-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	30-Dec-2004
Telephone Amendment	24-April-2005.
Telephone Amendment	27-April-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Nostrum Pharmaceuticals, Inc.
Address:	1800 N. Topping Avenue P.O. Box 33510 Kansas City, MO 64120-3510
Representative:	Paul T. Sudhakar
Address:	6739 Vahalla Ct Shawnee, KS 66217
Telephone:	(816) 507-8249
Fax	913-962-9061

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Carbamazepine

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Nostrum Pharmaceuticals proposed ANDA for Carbamazepine Extended-release Capsules is the reference listed drug Carbatrol® marketed by Shire Labs. As per the firm's statement, the two existing patents for the RLD will not be infringed by the product listed in this ANDA submission. Carbatrol® is not covered by any exclusivity.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Extended-release Capsules

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

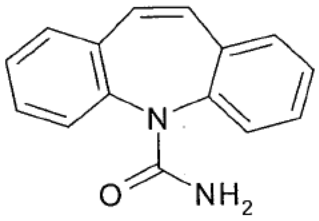
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 5H-dibenz[b,f]azepine-5-carboxamide
Molecular formula: $C_{15}H_{12}N_2O$

Molecular weight: 236.27
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	4/06/05	
	III			4	N/A		(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

17. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	5/13/04	S. Ferguson
Methods Validation	N/A		
Labeling	Acceptable	3/24/04	K.Lee
Bioequivalence	Acceptable	1/11/05	P. Nwakama
EA	Exclusion		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-697

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The drug product is prescribed as an anticonvulsant. No compendial monograph is available for the Extended-release Capsules. The drug product will be marketed in 30's and 120's packaging sizes. The firm proposes a 24 months expiration dating period.

Drug Substances: Carbamazepine is a white to off white powder, practically insoluble in water and soluble in alcohol and in acetone. The drug substance is a compendial USP item.

Formulation and Manufacturing Process: The drug product is manufactured by (b) (4) and filled in the size 0 opaque purple hard gelatin capsules. The size of the exhibit batch is (b) (4) capsules for the 300 mg strength. Proposed commercial batch size is (b) (4) capsules.

B. Description of How the Drug Product is Intended to be Used

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The firm needs to provide another drug product batch in order to adequately support the proposed manufacturing parameters. (b) (4) (b) (4) in the drug product is also requested.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-645/DMaldonado/

HFD-645/BArnwine/

HFD-617/YKong/

C. CC Block

ANDA 76-697
ANDA DUP
DIV FILE
Field Copy

Following this page, 31 pages were withheld in full - (b)(4)

3. The Division of Bioequivalence is being informed of these manufacturing concerns. Please contact the Division for any additional bioequivalence requirements.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-697
DIV FILE
Field Copy

Endorsements:

HFD-645/DMaldonado/4/28/05 DMR 5/23/05; DMR 6/22/05.

HFD-645 /BArnwine/5/20/05 for S. Bajpai 5-23-05

HFD-617/YKong/5/3/05 in 5/27/05

V:\FIRMSNZ\Nostrum\LTRS&REV\76697r3

F/T by: rad5/23/05

TYPE OF LETTER: APPROVE

#4

ANDA 76-697

Carbamazepine Extended-release Capsules USP, 300 mg

Nostrum Pharmaceuticals, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-697

2. REVIEW # 4

3. REVIEW DATE: April 17, 2006.

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Original Submission	26-Mar-2003
Amendment	20-May-2003
Amendment	12-Dec-2003
Amendment	30-Dec-2004
Telephone Amendment	24-April-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	22-Nov-2005
Correspondence	09-Mar-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Nostrum Pharmaceuticals, Inc.
Address:	505 Thornall St., #304 Edison, New Jersey 08837
Representative:	Paul T. Sudhakar
Address:	6739 Vahalla Ct. Shawnee, KS 66217
Telephone:	(816) 507-8249 or (913) 233-0054 ext. 101
Fax	913-962-9061

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Carbamazepine Extended-release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Nostrum Pharmaceuticals proposed ANDA for Carbamazepine Extended-release Capsules is the reference listed drug Carbatrol® marketed by Shire Labs. As per the firm's statement, the two existing patents for the RLD will not be infringed by the product listed in this ANDA submission. Carbatrol® is not covered by any exclusivity.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Extended-release Capsules

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

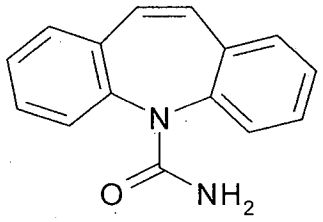
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 5H-dibenz[b,f]azepine-5-carboxamide
Molecular formula: $C_{15}H_{12}N_2O$
Molecular weight: 236.27
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	4/06/05	
	III			4	N/A		(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
				4			
				3,4			
				4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

17. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		

EES	Acceptable	5/13/04	S. Ferguson
Methods Validation	N/A		
Labeling	Acceptable	3/24/04	K.Lee
Bioequivalence	Acceptable	1/11/05	P. Nwakama
EA	Exclusion		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-697

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

In their November 22, 2005 amendment, the firm communicates their decision of not submitting a second exhibit batch as requested by the agency. Given the problems of the (b) (4) present in the exhibit batch along with (b) (4), the firm will need to provide the new test exhibit batch requested along with the required bio-studies. A deficiency is being issued.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The drug product is prescribed as an anticonvulsant. Nostrum formulation is an extended release dosage form that utilizes (b) (4) (b) (4) that controls release of the drug. The reference listed drug contains a mixture of immediate release, sustained release and enteric release pellets. The product is classified as a BCS Class II drug with high permeability and poor solubility. The drug product will be marketed in 30's and 120's packaging sizes. The firm proposes a 24 months expiration dating period.

Drug Substances: Carbamazepine is a white to off white powder, practically insoluble in water and soluble in alcohol and in acetone. The drug substance is a compendial USP item. Nostrum's formulation uses the (b) (4). Carbamazepine also (b) (4).

Formulation and Manufacturing Process: The drug product is manufactured by (b) (4) and filled in the size 0 opaque purple hard gelatin capsules. The size of the exhibit batch is (b) (4) capsules for the 300 mg strength. Proposed commercial batch size is (b) (4) capsules.

B. Description of How the Drug Product is Intended to be Used

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The company has to provide (b) (4) [redacted]

This by itself compromises the efficacy of the drug product.

(b) (4) [redacted]. The table below describes the key manufacturing steps, the acceptance criteria used in the exhibit batch and the acceptance criteria proposed for commercial lots:

Manufacturing	Manufacturing Step	Acceptance Criteria	Comments
(b) (4) [redacted]			

Following this page, 31 pages withheld in full - (b)(4)

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-697 APPLICANT: Nostrum Pharmaceuticals, Inc.

DRUG PRODUCT: Carbamazepine Extended-release Capsules USP, 300 mg

The deficiencies presented below represent MAJOR deficiencies.

We raised several questions relative to (b) (4) in the exhibit batch records in our June 27, 2005, Major Deficiency letter. We further emphasize these comments as follows:

> The Office of Generic Drugs uses data generated on the ANDA pivotal batch not only to demonstrate bioequivalence to the Reference Listed Drug, but also as a quality benchmark. Because of the importance of this batch, it is essential that details of its manufacture be unassailable. Since the manufacture of your exhibit batch, you have agreed to the addition of several critical drug product manufacturing process controls, including control of (b) (4)
>
> Therefore, please manufacture a new test batch and contact our Division of Bioequivalence for *in vivo* bioequivalence study requirements. Please also be advised that the adequacy of your manufacturing process controls will be further evaluated upon review of the new exhibit batch. Finally, it is also recommended that the root cause(s) of the (b) (4) problem be determined as well as identification of appropriate corrective measures in your next amendment.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-697

DIV FILE
Field Copy

Endorsements:

HFD-645/DMaldonado/4/17/06 done 4/20/06.

HFD-645/SFurness/4/18/06 M. Scott Furness 4/24/06

HFD-617/YKong/4/20/06 YK 4/25/06

V:\FIRMSNZ\Nostrum\LTRS&REV\76697R04.doc

F/T by: rad4/20/06

TYPE OF LETTER: NOT APPROVABLE

ANDA 76-697

Carbamazepine Extended Release Capsules, 300 mg

Nostrum Pharmaceuticals, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-697

2. REVIEW # 5

3. REVIEW DATE: July 31, 2007.

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Original Submission	20-May-2003
Amendments	12-Dec-2003
Amendment	30-Dec-2004
Telephone Amendment	24-April-2005
Telephone Amendment	27-April-2005
Amendment	22-Dec-2005
Correspondence	09-Mar-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	30-Mar-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Nostrum Pharmaceuticals, Inc.
Address:	1800 N. Topping Avenue P.O. Box 33510 Kansas City, MO 64120-3510
Representative:	Dhiren Shah
Telephone:	(816) 308-4970
Fax	816-841-4634

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Carbamazepine

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Nostrum Pharmaceuticals proposed ANDA for Carbamazepine Extended-release Capsules is the reference listed drug Carbatrol® marketed by Shire Labs. As per the firm's statement, the two existing patents for the RLD will not be infringed by the product listed in this ANDA submission. Carbatrol® is not covered by any exclusivity.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Extended-release Capsules

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

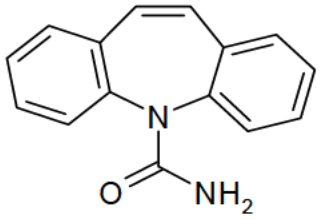
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 5H-dibenz[b,f]azepine-5-carboxamide
Molecular formula: $C_{15}H_{12}N_2O$
Molecular weight: 236.27
Structural Formula:

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1			
	III			4	N/A		(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

17. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Acceptable	3/24/04	K.Lee
Bioequivalence	Acceptable	1/11/05	P. Nwakama
EA	Exclusion		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-697

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

In their November 22, 2005 amendment, the firm communicated their decision of not submitting a second bio batch as requested by the Division. Given the problems with [redacted] (b) (4), the firm was again requested to provide the exhibit batch along with the required bio-studies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The drug product is prescribed as an anticonvulsant. Nostrum formulation is an extended release dosage form that utilizes [redacted] (b) (4) that controls release of the drug. The reference listed drug contains a mixture of immediate release, sustained release and enteric release pellets. The product is classified as a BCS Class II drug with high permeability and poor solubility. The drug product will be marketed in 30's and 120's packaging sizes. The firm proposes a 24 months expiration dating period.

Drug Substances: Carbamazepine is a white to off white powder, practically insoluble in water and soluble in alcohol and in acetone. The drug substance is a compendial USP item. Nostrum's formulation uses the [redacted] (b) (4). Carbamazepine also [redacted] (b) (4).

Formulation and Manufacturing Process: The drug product is manufactured by [redacted] (b) (4) and filled in the size 0 opaque purple hard gelatin capsules. The size of the exhibit batch is [redacted] (b) (4) capsules for the 300 mg strength. Proposed commercial batch size is [redacted] (b) (4) capsules.

B. Description of How the Drug Product is Intended to be Used

See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

The firm was requested to provide (b) (4) .

This by itself compromises the efficacy of the drug product.

(b) (4) The table below describes the key manufacturing steps, the acceptance criteria used in the exhibit batch and the acceptance criteria proposed for commercial lots:

Manufacturing	Manufacturing Step	Acceptance Criteria	Comments
			(b) (4)

Following this page, 32 pages withheld in full - (b)(4)

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-697 APPLICANT: Nostrum Pharmaceuticals, Inc.

DRUG PRODUCT: Carbamazepine Extended-release Capsules, 300 mg

The deficiencies presented below represent MAJOR deficiencies.

Please be aware that the Office of Generic Drugs uses data generated on the ANDA pivotal batch not only to demonstrate bioequivalence to the Reference Listed Drug, but also as a quality benchmark. Because of the importance of this batch, it is essential that details of its manufacture be unassailable. We acknowledge the changes and emphasis placed in the (b) (4) As mentioned in previous communications, the apparent (b) (4) renders the original bioequivalence batch as inappropriate for *in-vivo* bioequivalence studies. We reiterate our previous request for submission of a new bioequivalence study as delineated in our last deficiency letter. Please also contact our Division of Bioequivalence for the appropriate *in vivo* bioequivalence study requirements. Should you wish to communicate with the Division by means of a teleconference, please contact the CMC review team project manner regarding this matter.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-697

DIV FILE
Field Copy

Endorsements:

HFD-645/DMaldonado/7/31/07

HFD-645/SFurness/8/8/07

HFD-617/Tliu/8/8/07

V:\FIRMSNZ\Nostrum\LTRS&REV\76697R05

F/T by:

TYPE OF LETTER: NOT APPROVABLE

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

/s/

Damaris Maldonado
8/9/2007 08:47:42 AM
CHEMIST

Theresa Liu
8/13/2007 08:42:22 AM
CSO

Michael S Furness
8/13/2007 08:48:43 AM
CHEMIST

ANDA 76-697

Carbamazepine Extended Release Capsules
100 mg, 200 mg, 300 mg

Nostrum Pharmaceuticals, LLC
(formerly Nostrum Pharmaceuticals, Inc.)

Latiff Hussain Ph.D.
Office of Generic Drugs, Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-697

2. REVIEW # 6

3. REVIEW DATE: November 3, 2008; December 4, 2008 (updated)

This ANDA was transferred on August 19, 2008 from Team 7 (DC II) to Team 11 (DCIII) and was assigned to this reviewer on September 22, 2008.

4. REVIEWER: Latiff Hussain

Note: CR #1 through CR #5 was completed by Damaris Maldonado*

**Chemistry Review*

5. PREVIOUS DOCUMENTS:

Original Submission	20-May-2003
Amendments	12-Dec-2003
Amendment	30-Dec-2004
Telephone Amendment	24-April-2005
Telephone Amendment	27-April-2005
Amendment	22-Dec-2005
Correspondence	09-Mar-2006
Amendment	30-Mar-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment	28-April-2008
Correspondence	24-Sep-2008
Gratuitous Amendment (EDR)	10-Oct-2008
Amendment (EDR)	22-NOV-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Nostrum Pharmaceuticals, LLC.

Chemistry Review Data Sheet

Mailing Address:	1800 N Topping Ave Kansas City MO 64120 TEL: 732 635 0036 ext 102 Fax: 816 841 4634
Representative:	Theodore R. Miro 505 Thornall St. Suite 304, Edison NJ 08837 TEL: (816) 308-4902 FAX: (816) 308-4975

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Carbamazepine

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Nostrum Pharmaceuticals proposed ANDA for Carbamazepine Extended-release Capsules is the reference listed drug Carbatrol® marketed by Shire Labs. As per the firm's statement, the two existing patents for the RLD will not be infringed by the product listed in this ANDA submission. Carbatrol® is not covered by any exclusivity.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Extended-release Capsules

12. STRENGTH/POTENCY: 100 mg , 200 mg, 300 mg

13. ROUTE OF ADMINISTRATION: Oral

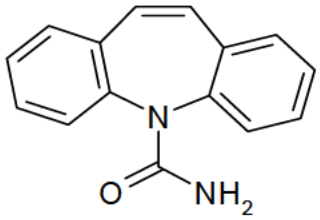
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 5H-dibenz[b,f]azepine-5-carboxamide
Molecular formula: $C_{15}H_{12}N_2O$
Molecular weight: 236.27
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Not adequate	10/31/2008	Latiff Hussain
	III			4	N/A		(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

17. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Acceptable	10/15/2008	Melanie Shin
Bioequivalence	Acceptable	12/3/2008	Aaron Sigler
EA	Exclusion		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-697

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry section is NOT approvable (minor). Bioequivalence is ACCEPTABLE. Labeling is ACCEPTABLE. EER: PENDING

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The drug product is prescribed as an anticonvulsant. Nostrum formulation is an extended release dosage form that utilizes a (b) (4) that controls release of the drug. The reference listed drug contains a mixture of immediate release, sustained release and enteric release pellets. The product is classified as a BCS Class II drug with high permeability and poor solubility. The drug product will be marketed in 30's and 120's packaging sizes. The firm proposes a 24 months expiration dating period.

Drug Substances: Carbamazepine is a white to off white powder, practically insoluble in water and soluble in alcohol and in acetone. The drug substance is a compendial USP item. Nostrum's formulation uses the (b) (4). Carbamazepine also (b) (4).

Formulation and Manufacturing Process: The drug product is manufactured by (b) (4) and filled in the size 0 opaque purple hard gelatin capsules (300 mg), size 1 opaque standard yellow hard gelatin capsules (200 mg) or size 2 dark green opaque hard gelatin capsules (100 mg) .

B. Description of How the Drug Product is Intended to be Used

The maximum recommended dosing is 1600 mg/day.

	IT	QT
Drug substance* (ICH Q3A)	(b) (4)	

Drug product (ICHQ3B)	(b) (4)

*listed in the USP
See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

In CR #4 a MAJOR Deficiency was identified with regard to original bio batch (Lot # (b) (4) This raised concerns about the manufacturing process and the (b) (4), and hence it was not possible to justify the proposed manufacturing process for commercial production. Therefore, the firm was asked to manufacture a new test/exhibit batch and contact the Division of Bioequivalence for *in vivo* bioequivalence study requirements for the same. In response to the request, the firm, in its March 30, 2007 amendment, provided details of manufacture of a new test/exhibit batch (lot # NP07-601) including the changes and emphasis placed on the (b) (4) of the new exhibit lot, # NP07-601. Additionally, comparative *in-vitro* studies between the original bio batch #020313 and the new exhibit lot # NP07-601 was provided. However, the firm stated that a new *in vivo* bioequivalence study is not needed as in its opinion the original bioequivalence study (with Lot # 020313) proved that the test product was bioequivalent to the RLD. However, following the review of the March 30, 2007 amendment in CR #5, the agency reiterated the request for submission of a new bioequivalence study and was also informed by the agency that a detailed CMC review will be undertaken only after a the re-made bio-batch is found to be bioequivalent to the RLD which the firm acknowledged in its April 28, 2008 cover letter. In the April 28, 2008 MAJOR AMENDMENT which is the subject of CR #6, the firm informed the agency that it has completed all three bioequivalence studies (to be evaluated by DBE) per agency's instructions. Additionally, the firm informed the agency that it has developed dose-proportional 100 mg and 200 mg strength capsules and it intends to amend the ANDA with a request for bio-waiver for these two lower strengths. New 300 mg pivotal/stability batch (B070068), 200 mg batch (B070046B), and 100 mg batch (B070046A) batch was manufactured and details of the same were provided in the amendment.
Following the CMC review of April 28, 2008 MAJOR AMENDMENT and October 10, 2008 Gratuitous amendment, the following conclusion was reached:

- Chemistry section is DEFICIENT due to inadequacies in the drug substance specifications and drug product release and stability specifications.
- Bioequivalence is ACCEPTABLE.
- EER: PENDING

Following this page, 39 pages withheld in full - (b)(4)

- (b) (4)

8. Please provide all stability data accrued till date.

9. A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval.

10. We request you to provide an electronic copy, in addition to the paper copy, of the summary of response to the agency's questions, provided in this deficiency letter. The relevant attachments and the body of data related to the amendment may be submitted in the same format as your original application.

Sincerely,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsement Block

L. Hussain, Ph.D./11/3/08; 12/4/08 (updated)
A. Srinivasan,Ph.D./12/10/08
L. Kwok, Pharm.D./12/11/08

V:\Chemistry Division III\Team 11\Final Version For DFS\Latiff\76697R06.doc

NA MINOR

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

/s/

Latiff Hussain
12/12/2008 06:03:51 PM
CHEMIST

Lisa Kwok
12/15/2008 09:55:51 AM
CSO

Aloka Srinivasan
12/15/2008 10:11:42 AM
CHEMIST

ANDA 76-697

Carbamazepine Extended Release Capsules
100 mg, 200 mg, 300 mg

Nostrum Pharmaceuticals, LLC
(formerly Nostrum Pharmaceuticals, Inc.)

Latiff Hussain Ph.D.
Office of Generic Drugs, Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-697

2. REVIEW # 7

3. REVIEW DATE: March 31, 2009; 9/9/09 (updated for amendments)

This ANDA was transferred on August 19, 2008 from Team 7 (DC II) to Team 11 (DCIII) and was assigned to this reviewer on September 22, 2008.

4. REVIEWER: Latiff Hussain

Note: CR #1 through CR #5 was completed by Damaris Maldonado*

**Chemistry Review*

5. PREVIOUS DOCUMENTS:

Original Submission	20-May-2003
Amendments	12-Dec-2003
Amendment	30-Dec-2004
Telephone Amendment	24-April-2005
Telephone Amendment	27-April-2005
Amendment	22-Dec-2005
Correspondence	09-Mar-2006
Amendment	30-Mar-2007
Major Amendment	28-April-2008
Correspondence	24-Sep-2008
Gratuitous Amendment (EDR)	10-Oct-2008
Amendment (EDR)	22-Nov-2008

6. SUBMISSION(S) BEING REVIEWED:

Amendment (EDR)	15-Jan-2009
Amendment (EDR)	26-Mar-2009
Telephone Amendment (EDR)	20-July-2009
Telephone Amendment (EDR)	17-Aug-2009
Telephone Amendment (EDR)	03-Sep-2009

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Nostrum Pharmaceuticals, LLC.
Mailing Address:	1800 N Topping Ave Kansas City MO 64120 TEL: 732 635 0036 ext 102 Fax: 816 841 4634
Representative:	Theodore R. Miro 505 Thornall St. Suite 304, Edison NJ 08837 TEL: (816) 308-4902 FAX: (816) 308-4975

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Carbamazepine

9. LEGAL BASIS FOR SUBMISSION:

The basis for the Nostrum Pharmaceuticals proposed ANDA for Carbamazepine Extended-release Capsules is the reference listed drug Carbatrol® marketed by Shire Labs. As per the firm's statement, the two existing patents for the RLD will not be infringed by the product listed in this ANDA submission. Carbatrol® is not covered by any exclusivity.

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Extended-release Capsules

12. STRENGTH/POTENCY: 100 mg , 200 mg, 300 mg

13. ROUTE OF ADMINISTRATION: Oral

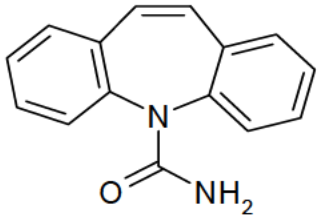
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 5H-dibenz[b,f]azepine-5-carboxamide
Molecular formula: $C_{15}H_{12}N_2O$
Molecular weight: 236.27
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate (IR)	3/31/2009	Latiff Hussain
	III			4	N/A		(b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

17. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		

EES	**WITHOLD**	2/9/2009	C. CRUZ
Methods Validation	N/A		
Labeling	Acceptable	6/25/2009	Melanie Shin
Bioequivalence	Acceptable	12/3/2008	Aaron Sigler
EA	Exclusion		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-697

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC review is currently acceptable per the review team recommendations. ANDA approvability is pending Division review, other disciplines and/or EES. This CMC review may require an addendum based on recommendations made by other review disciplines.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The drug product is prescribed as an anticonvulsant. Nostrum formulation is an extended release dosage form that utilizes a (b) (4) that controls release of the drug. The reference listed drug contains a mixture of immediate release, sustained release and enteric release pellets. The product is classified as a BCS Class II drug with high permeability and poor solubility. The drug product will be marketed in 30's and 120's packaging sizes. The firm proposes a 24 months expiration dating period.

Drug Substances: Carbamazepine is a white to off white powder, practically insoluble in water and soluble in alcohol and in acetone. The drug substance is a compendial USP item. Nostrum's formulation uses the (b) (4). Carbamazepine also (b) (4).

Formulation and Manufacturing Process: The drug product is manufactured by (b) (4) and filled in the size 0 opaque purple hard gelatin capsules (300 mg), size 1 opaque standard yellow hard gelatin capsules (200 mg) or size 2 dark green opaque hard gelatin capsules (100 mg) .

B. Description of How the Drug Product is Intended to be Used

The maximum recommended dosing is 1600 mg/day.

	IT	QT
Drug substance* (ICH Q3A)		(b) (4)

Drug product (ICHQ3B)		(b) (4)

*listed in the USP
See Labeling.

C. Basis for Approvability or Not-Approval Recommendation

- The CMC review is currently acceptable per the review team recommendations. ANDA approvability is pending Division review, other disciplines and/or EES. This CMC review may require an addendum based on recommendations made by other review disciplines.
- Bioequivalence is ACCEPTABLE.
- Labeling is ACCEPTABLE
- **EER: WITHOLD**

Endorsement Block

L. Hussain, Ph.D./3/31/2009;5/11/09; 9/9/09 (update)
A. Srinivasan,Ph.D./4/21/09;5/11/09
L. Kwok, Pharm.D./4/21/09; 6/25/09

V:\Chemistry Division III\Team 11\Latiff\76697R07.doc

Following this page, 65 pages withheld in full - (b)(4)

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT: NONE

Tmax information about proposed formulation and reference product:

Chemistry contacted DBE to address potential Tmax issues between the proposed formulation and reference product, see details next page:

From: Srinivasan, Aloka
Sent: Wednesday, April 01, 2009 7:45 AM
To: Davit, Barbara M
Cc: Sayeed, Vilayat A; Gill, Devinder; Hussain, Latiff
Subject: FW: Update: Carbamazepine ER Capsules, 100 mg, 200 mg and 300 mg, ANDA 76-697

Hi Barbara,
This is regarding carbamazepine ER capsules from Nostrom, ANDA 76697.

Please refer to Vilayat's email below regarding the tmax.

In view of the difference in design of the RLD and this generic product (IR, ER and DR in RLD vs. only ER in generic), we are being cautious about this.
Thanks a lot,
Regards,
Aloka

Aloka Srinivasan, Ph. D.
Team Leader, HFD 630
Office of Generic Drugs,
Division of Chem III, Team 11
MPN II, Room E135
7500 Standish Place
Rockville, MD 20855

Phone: 240-276-8487
Fax: 240-276-8474

Excellence is our standard

From: Sayeed, Vilayat A
Sent: Wednesday, April 01, 2009 6:40 AM
To: Hussain, Latiff; Srinivasan, Aloka
Cc: West, Robert L; Gill, Devinder
Subject: RE: Update: Carbamazepine ER Capsules, 100 mg, 200 mg and 300 mg, ANDA 76-697 - Minor Amendment dated January 15, 2009

Aloka/Latiff

The NDA for this DP has IR/DR/ER beads in the capsule and as you know the ANDA is manufactured with ER beads only. Based on the concern of this product therapeutic, please request bio to check on the relevance of tmax in this product line and provide a memorandum on their findings. We will need this information to move the application forward. Thanks

Vilayat

Vilayat A. Sayeed, Ph.D.
Director, Division of Chemistry III
FDA/CDER/OPS/OGD
7500 Standish Place
MPN II Rockville, MD 20855
Office (240) 276-8486, fax (240) 276-8474
Vilayat.Sayeed@FDA.HHS.GOV
Excellence is Our Standard

DBEs evaluation of potential Tmax issues between the proposed formulation and reference product (excerpted from DBE review dated 4/28/2009 by Kimberly W Raines) is as follows:

Review of Bioequivalence Studies for Tmax differences

1 EXECUTIVE SUMMARY

Carbatrol® (carbamazepine) extended-release capsules (NDA 20-712) were approved in 1997 as an anticonvulsant and specific analgesic for trigeminal neuralgia. Carbatrol® is formulated as a capsule consisting of immediate release, extended release, and enteric release beads. Recent attention has shed light on possible differences in Tmax values between generic formulations of carbamazepine extended-release capsules and reference listed drug (RLD). It is suggested that significant differences in Tmax may render generic products not therapeutically equivalent to the RLD.

At the request of the Division of Chemistry 3, the Division of Bioequivalence (DBE) 2 investigated possible Tmax differences between Nostrum's Carbamazepine Extended Release Capsules, 300 mg and the RLD, Carbatrol®, ER Capsules 300 mg, manufactured by Shire US. The DBE 2 reviewed Tmax values obtained in the fasting, fed, and fasting sprinkle *in vivo* bioequivalence (BE) studies submitted by Nostrum on April 28, 2008 in ANDA #76697.

Upon review it was determined that for the fasting and fasting sprinkle BE studies, the test product Tmax median values are not significantly different from the Tmax of the RLD, demonstrating a T/R ratio of 1.04 and 1.08, respectively. It is also noted that the mean plasma concentration curves of the test and reference products are almost super imposable for the fasting and fasting sprinkle BE studies.

In the fed BE study, the median Tmax does appear to be different than that of the RLD, 21 hours for the test and 14 hours for the reference product. The T/R ratio for the fed BE study is 1.50. In the fed BE study 8 subjects (N=21) demonstrated significantly different (> 8 hr) Tmax values between the test and reference products.

The RLD label[1] states, "A high fat meal diet increased the rate of absorption of a single 400 mg dose (mean T_{max} was reduced from 24 hours, in the fasting state, to 14 hours and C_{max} increased from 3.2 to 4.3 µg/mL) but not the extent (AUC) of absorption. Carbatrol® can be taken with or without meals."

Therefore the DBE 2 does not consider the difference in median Tmax values between the test product and RLD in the fed BE study to be of clinical significance, as the Tmax values fall within the limits set forth in the label.

It should be noted that the test product, Nostrum's Carbamazepine Extended-Release Capsules, do not demonstrate a food effect (i.e. a significant reduction in Tmax under fed conditions), as indicated in the RLD label and demonstrated in the submitted *in vivo* bioequivalence studies. The Labeling Division should be aware of this matter, as the Nostrum product could not support the RLD label.

The application is complete. A letter to the firm is not needed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE

/s/

LATIFF A HUSSAIN
09/10/2009

ALOKA SRINIVASAN
09/10/2009

LISA H KWOK
09/10/2009

ANDA: 077699

Review #: Addendum to Review 7

Drug: **Carbamazepine Extended Release Capsules 100 mg, 200 mg, 300 mg**

Firm: Nostrum Pharmaceuticals, LLC

Reviewer: **Latiff Hussain, Ph.D.**
Office of Generic Drugs
Division of Chemistry III

Background:
CMC was found acceptable on 9/10/2009 when labeling was found acceptable on 6/25/2009. However labeling approval summary (#3) was updated to include Nostrum's subsequent labeling amendments dated 9/29/2009 and 10/6/2009 to include revision of the "Food Effect" section of its Prescribing Information to read:

Food Effect:
The multiple dose study conducted in the fed state showed that the steady-state Cmax values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

Assessment: Adequate
Labeling has found the above revision acceptable on 11/2/2009 (approval summary (#3)) by Melanie Shin.

CMC is ACCEPTABLE; USP <467> compliant; BIO EQUIVALENCE, LABELING are ACCEPTABLE; EER on WITHOLD

Endorsements:

HFD-630/Latiff Hussain, Ph.D./Chemistry Reviewer/6/8/2010
HFD-630/Dave Gill, Ph.D./Division Director/

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE

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/s/

LATIFF A HUSSAIN
06/08/2010

DEVINDER S GILL
06/08/2010

ANDA 076697

Carbamazepine Extended Release Capsules
100 mg, 200 mg, 300 mg

Nostrum Pharmaceuticals, LLC
(formerly Nostrum Pharmaceuticals, Inc.)

Addendum #2 to R07
Team 33
Office of Generic Drugs, Division of Chemistry III

Chemistry Assessment Section

Review of Minor Amendment Dated February 7, 2011

Background:

The firm submitted an amendment dated February 17, 2011 in response to Agency's correspondence dated July 19, 2010. The Amendment in eCTD format includes the following:

- cGMP Status Change Certification
- Chemistry Changes Update
- Final Printed labeling

Nostrum is requesting full approval of this ANDA.

CMC Assessment:

cGMP Status Change:

Nostrum was informed on February 11, 2010 that as a result of recent inspection conducted from October 13, 2010 to November 5, 2010 on NLI facility, the cGMP status has been changed from "OAI" to "VAI". The certification is provided (P.3.1).

Chemistry Changes Update:

The firm has made minor changes which do not alter the previously submitted manufacturing process requirements. Summary of updated CMC information is reported in the following table:

Controls	Document submitted	Submission type/date	Change	Comments
(b) (4)		Minor Amendment 1/15/09	No change	NA
		Telephone Amendment, 3/26/09	No change	NA
		Telephone Amendment, 9/3/09	No change	NA
		Telephone Amendment, 9/3/09	No change	NA
		Telephone Amendment, 9/3/09	No change	NA

(b) (4)	Telephone Amendment, 9/3/09	Summarized within Section 1.13.5.	(b) (4)
	Telephone Amendment, 9/3/09		
	Telephone Amendment, 9/3/09		
	Telephone Amendment, 9/3/09		
	Amendments: 4/28/08 10/10/08		Updated to comply with USP/NF monographs and for editorial changes.
	Major Amendment: 4/28/08		Updated with specific instructions to comply with internal QA procedures and for editorial changes.

All the changes have been incorporated prior to the last two CMC reviews dated June 8, 2010 and September 10, 2009. **In the last review dated June 8, 2010 the CMC was found acceptable at the reviewer and the division level.**

In addition, the firm has submitted 36 month RT stability data for submission batches of all three strengths. The firm is proposing an expiration date of (b) (4) at the time of approval. The firm has **not** submitted stability data for three commercial batches to support expiration date of (b) (4) (b) (4)

The drug product should be granted 2 years of "Tentative Expiration Date" on the basis of current data. The expiration date will be confirmed post approval, after acceptable data is generated for three commercial batches. Extension of expiration date cannot be considered at the present time.

Comment: The firm will be asked to acknowledge the tentative expiration date of 2 years.

List of Deficiencies to Be Communicated (None)

Endorsement
HFD-630/S. Patankar /Team Leader /
HFD-630/V. Sayeed/Division Director/

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TYPE OF LETTER: APPROVABLE

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/s/

SUHAS J PATANKAR
02/23/2011

VILAYAT A SAYEED
02/24/2011

ANDA 076697

Carbamazepine Extended Release Capsules
100 mg, 200 mg, 300 mg

Nostrum Pharmaceuticals, LLC
(formerly Nostrum Pharmaceuticals, Inc.)

Addendum #3 to R07
Team 33
Office of Generic Drugs, Division of Chemistry III

Background:

This addendum summarizes the status updates since the DARRTs check in of Addendum #2 to Review #7 on February 24, 2011.

CMC: Adequate as of 2/24/11

Labeling: Adequate as of 4/05/11

EES: Acceptable as of 4/18/11

Endorsement
HFD-630/S. Patankar /Team Leader /
HFD-630/V. Sayeed/Division Director/

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TYPE OF LETTER: APPROVABLE

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/s/

SUHAS J PATANKAR
04/28/2011

VILAYAT A SAYEED
05/18/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-697

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-697
Drug Product Name	Carbamazepine Extended Release Capsules
Strength	300 mg
Applicant Name	Nostrum Pharmaceuticals, Inc.; c/o Martec Pharmaceutical, Inc.
Address	1800 N. Topping, Kansas City, MO 64120
Submission Date(s)	March 26, 2003
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsNZ \ Nostrum\ltrs&rev\76697N0303.doc

I. Executive Summary

This submission consisted of two (fasting and non-fasting) bioequivalence (BE) studies and dissolution data on the 300 mg strength. Both studies are two-way, crossover studies conducted in healthy adult males and females (fasting, n = 26; non-fasting, n = 18). Statistical analyses of the plasma concentration data for carbamazepine and carbamazepine 10, 11-epoxide in both studies demonstrate bioequivalence. Although the DBE recommends the measurement of only the parent drug, carbamazepine, the firm included statistically analyzed the PK data for the metabolite, carbamazepine 10, 11-epoxide and submitted the data for informational purpose.

Carbamazepine results in the fasting study are (point estimate, 90% CI): LAUCT of 1.02, 93.2 – 111.1%; LAUCI 1.02, 93.6 – 110.4%; and LCmax 0.96, 89.5 – 103.0%.
Carbamazepine 10, 11-epoxide results in the fasting study are (point estimate, 90% CI): LAUCT of 1.01, 91.1 – 112.1%; LAUCI 1.02, 93.9 – 110.1%; and LCmax 0.98, 90.0 – 106.8%.

Carbamazepine results in the non-fasting study are (point estimate, 90% CI): LAUCT of 0.88, 80.3 – 95.4%; LAUCI 0.89, 81.8 – 95.8%; and LCmax 0.80, **74.7** – 86.7%.
Carbamazepine 10, 11-epoxide results in the non-fasting study are (point estimate, 90% CI): LAUCT of 0.82, **72.3** – 93.2%; LAUCI 0.86, **78.1** – 94.6%; and LCmax 0.83, **75.2** – 91.0%. The study is acceptable because it was initiated on August 10, 2002, and it meets the acceptance criteria in place at that time.

The firm did not conduct the dissolution testing according to the FDA-recommended method and specifications. The firm did not conduct the additional fasting BE (Sprinkle) study. Therefore, the application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Carbamazepine ER Capsules, 300 mg
Reference Product	Carbatrol® XL Capsules, 300 mg
RLD Manufacturer	Shire Pharmaceutics
NDA No.	20712
RLD Approval Date	September 30, 1997
Indication	Anticonvulsant and treatment of trigeminal neuralgia

B. PK/PD Information

Bioavailability	Linear pharmacokinetics over single dose range of 200 – 800 mg.
Food Effect	Tmax reduced (24 hours to 14 hours) and Cmax increased (3.2 - 4.3 mcg/mL). AUC not affected by food. *Based on the RLD labeling, the pharmacokinetic profile of ER carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.*
Tmax	30 – 42 hours
Metabolism	Primarily metabolized by hepatic CYP 3A4 to carbamazepine-10, 11-epoxide; autoinduction leads to wide variability in half-life.
Excretion	Renally (72% as unconjugated metabolites and only about 3% as unchanged drug) and 25% excreted in the feces.
Half-life	35 – 40 hours
Relevant OGD or DBE History	No controlled documents, protocols or ANDAs have previously been submitted for carbamazepine ER capsules. Two ANDAs (# (b) (4) and # (b) (4)) have been submitted for carbamazepine ER tablets and ANDA # (b) (4) has been found acceptable by the DBE.
Agency Guidance	CDER 2002 BA/BE guidance
Drug Specific Issues	The NDA (bioequivalence) study included the determination of carbamazepine as well as its active metabolite carbamazepine epoxide. A sprinkle fasting study was also conducted.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
Applesauce Sprinkling	**No**	**0**
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

Vol. 1.4, Vol. 2009 - 2076		
	Parent	**Metabolite**
Analyte name	Carbamazepine	Carbamazepine 10, 11-Epoxide
Internal Standard	(b) (4)	(b) (4)
Method description	LC/MS/MS	LC/MS/MS
QC range	0.20 to 7.00 mcg/mL	0.02 to 0.70 mcg/mL
Standard curve range	0.10 to 10.00 mcg/mL	0.01 to 1.00 mcg/mL
Limit of quantitation	0.10 mcg/mL	0.01 mcg/mL
Average recovery of Drug (%)	79.0%	49.9%
Average Recovery of Int. Std (%)	91.9%	91.9%
Intraday precision range (%CV)	0.8 to 3.7%	1.6 to 5.6%
Intraday accuracy range (%)	92.5 to 102.0%	90.0 to 103.0%
Intraday precision range (%CV)	1.2 to 3.4%	3.3 to 5.3%
Intraday accuracy range (%)	95.5 to 101%	95.0 to 100.0%
Interday precision range (%CV)[STD]	1.0 to 4.2%	1.1 to 10.0%
Interday accuracy range (%)[STD]	96.0 to 104.0%	98.0 to 104.0%
Bench-top stability (hrs)	24 hours	24 hours
Stock stability (days)	66 days	66 days
Processed stability (hrs)	72 hours	72 hours
Freeze-thaw stability (cycles)	3 cycles	3 cycles
Long-term storage stability (days)	153 day	153 days
Dilution integrity	2 to 4-fold, 107 to 101%	2 to 4-fold, 110.0 to 102%
Specificity	Yes	Yes
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes
20% Chromatograms included (Y/N)	Yes	Yes
Random Selection of Serial Chrom	Yes	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	PRACS R02-733
Study Design	Randomized, Single-Dose, 2-way Crossover, Relative Bioavailability Study
No. of subjects enrolled	26
No. of subjects completing	24 (Subjects #6 and #11 elected to withdraw)
No. of subjects analyzed	22
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 17 Female: 9
Test product	Carbamazepine ER Capsules
Reference product	Carbatrol® Capsules
Strength tested	300 mg
Dose	1 x 300 mg

Summary of Statistical Analysis (Carbamazepine) Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.02	93.2 – 111.1%
AUC_{∞}	1.02	93.6 – 110.4 %
C_{max}	0.96	89.5 – 103.9 %

Summary of Statistical Analysis (Carbamazepine 10, 11-epoxide) Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.01	91.1 – 112.1%
AUC_{∞}	1.02	93.9 – 110.1
C_{max}	0.98	90.0 – 106.8

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic Repeats	0	0	0	0	0	0	0	0
Low Internal Standard	10	12	1.08	1.30	10	12	1.08	1.30
Laboratory Accident	2	0	0.22	0	2	0	0.22	0
Total	**12**	**12**	**1.30**	**1.30**	**12**	**12**	**1.30**	**1.30**

Did use of recalculated plasma concentration data change study outcome? No

Comments on Fasting Study: Acceptable.

2. Single-dose Fed Bioequivalence Study

Study No.	PRACS R02-734
Study Design	Randomized, Single-Dose, 2-way Crossover, Relative Bioavailability Study
No. of subjects enrolled	18
No. of subjects completing	18
No. of subjects analyzed	18
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 13 Female: 5
Test product	Carbamazepine ER Capsules
Reference product	Carbatrol® Capsules
Strength tested	300 mg
Dose	1 x 300 mg

Summary of Statistical Analysis (Carbamazepine) Additional Information in Appendix, Table 17 and Table 18		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.88	80.3 – 95.4%
AUC_{∞}	0.89	81.8 – 95.8%
C_{max}	0.80	**74.7** – 86.7%

Summary of Statistical Analysis (Carbamazepine 10, 11-expoxide) Additional Information in Appendix, Table 17 and Table 18		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.82	72.3 – 93.2%
AUC_{∞}	0.86	78.1 – 94.6%
C_{max}	0.83	**75.2** – 91.0%

Reanalysis of Study Samples Additional information in Appendix, Table 16								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic Repeats	0	0	0	0	0	0	0	0
Low Internal Standard	20	14	2.79	1.95	20	14	2.79	1.95
Laboratory Accident	2	0	0.28	0	2	0	0.28	0
Diluted QC Sample	1	3	0.14	0.42	1	3	0.14	0.42
Total	23	17	3.21	2.37	23	17	3.21	2.37

Did use of recalculated plasma concentration data change study outcome? No

Comments on fed study: The fed study is acceptable.

F. Formulation

Location in appendix	Section B, Page 24
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored? (yes or no)	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm's Method
Medium	Aqueous pH buffer with 1% SLS (pH 1.2, 4.5, 6.0 and 7.5) and Water
Volume (mL)	900 mL
USP Apparatus type	Apparatus I (Basket)
Rotation (rpm)	100 rpm
Firm's proposed specifications	N/A
FDA-recommended specifications	N/A
F2 metric calculated (yes or no)	No
If no, reason why F2 not calculated	Non- comparative
Method is acceptable (yes or no)	No

F2 metric, other strengths compared to biostudy strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A			

F2 metric, test compared to reference	
Strength	F2 metric
N/A	

H. Waiver Request(s)

Strengths for which waivers requested	None
Regulation cited	N/A
Proportional to strength tested in vivo (yes or no)	N/A
Dissolution is acceptable (yes or no)	No
Waiver granted (yes or no)	N/A

I. Deficiency Comments

1. The RLD labeling allows for the capsule to be opened and the beads sprinkled over applesauce. The firm has not submitted a fasting study with the capsule administered as sprinkle over applesauce.

2. The dissolution testing conducted by the firm is incomplete (see Nhan Tran's attached e-mail). It should conduct comparative dissolution testing of the test and reference products using:

   a) USP Apparatus I (Basket) at 100 rpm in 900 ml water, pH 1.2, 4.5 and 6.8 with and without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs.

   b) USP Apparatus II (Paddle) at 50 rpm and 75 rpm in 900 ml water, pH 1.2, 4.5 and 6.8 with and without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs.

   c) In addition, the firm is suggested to use the following FDA recommended dissolution method:

      USP Apparatus II (Paddle) at 75 RPM
      Medium: 900 ml of dissolution media
      First 4 hrs: pH 1.1 HCl
      After 4 hrs: pH 7.5 phosphate buffer with 0.1% SLS
      Sampling times: 1, 4, 6 and 12 hrs.

The use of higher SLS concentration should be justified and fully documented.

J. Recommendations

1. The single-dose, fasting bioequivalence study conducted by Shire Richwood's on the test product, Carbamazepine ER Capsules, 300 mg, lot # 020313, comparing it with the reference product, Shire Richwood's Carbatrol® XL Capsules, 300 mg, lot # GY41, has been found acceptable by the Division of Bioequivalence. The test product, Shire Richwood's Carbamazepine ER Capsules, 300 mg, is deemed bioequivalent to the reference product, Shire Richwood's Carbatrol® XL Capsules, 300 mg, under fasting conditions.

2. The single-dose, non-fasting bioequivalence study conducted by Shire Richwood's on the test product, Carbamazepine ER Capsules, 300 mg, lot # 020313, comparing it with the reference product, Shire Richwood's Carbatrol® XL Capsules, 300 mg, lot # GY41, has been found acceptable by the Division of Bioequivalence. The test product, Shire Richwood's Carbamazepine ER Capsules, 300 mg, is deemed bioequivalent to the reference product, Shire Richwood's Carbatrol® XL Capsules, 300 mg, under non-fasting conditions.

3. The *in vitro* dissolution testing conducted by Shire Richwood on its Carbamazepine ER Capsules, 300 mg, has been found incomplete because of cited deficiency #2.

4. The ANDA submission is incomplete because the firm did not conduct a fasting bioequivalence study with the drug product administration as sprinkled over applesauce.

1/29/2004

Patrick Nwakama, Pharm.D. Branch III Date signed

FOR 1/29/2004

Gur Jai Pal Singh, Ph.D. Branch III Date signed

1/29/04

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	PRACS R02-733
Study Title	Randomized, Single-Dose, 2-way Crossover Bioequivalence Study of Martec and Shire (Carbatrol®) 300 mg Carbamazepine ER Capsules under Fasting Conditions
Clinical Site	PRACS Institute, Ltd., Fargo, North Dakota
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Period I: August 10 – 20, 2002 Period II: September 7 – 17, 2002
Analytical Site	(b) (4)
Analytical Director	(b) (6) M.S.
Analysis Dates	September 27 – October 22, 2002
Storage Period	73 days [Long-term Stability: 153 days]

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Carbamazepine ER	Carbatrol® Capsules
Manufacturer	Martec	Shire Richwood, Inc.
Batch/Lot No.	020313	GY41
Manufacture Date	3/27/2002	N/A
Expiration Date	N/A	02/03
Strength	300 mg	300 mg
Dosage Form	Capsules	Capsules
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.59% (RSD: 0.39%)	102.07% (RSD: 0.22%)
Content Uniformity	100.62% (RSD: 0.92%)	101.72% (RSD: 1.80%)
Formulation	See Appendix Section B	
Dose Administered	1 x 300 mg	1 x 300 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	28 days
Randomization Scheme	AB: 1,2,3,6,8,13,17,18,19,21,23,24,25 BA: 4,5,7,9,10,11,12,14,15,16,20,22,26
Blood Sampling Times	0, 2,5,8,12,16,20,24,26,28,30,32,34,36,38,48,72,120, 168,192, and 240 hours
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	- 20^0 C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours
Length of Confinement	48 hours
Safety Monitoring	Subjects were monitored throughout the confinement portion of the study. Vital signs were taken prior to dosing and as scheduled post-dosing.

Table 1 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	96.1
Mean	27.7	Mean	77.3	18-40	84.6	Male	65.4	Afr. Amer.	3.9
SD	11.4	SD	10.3	41-64	15.4	Female	34.6	Hispanic	
Range	18 – 62	Range	53.6 – 94.9	65-75				Asian	
				>75				Others	

Study Results

Table 2 Dropout Information

Subject No	Subject #6	Subject #11	Subject #20	Subject #22
Reason	Withdrew for personal reasons	Withdrew for personal reasons	Failed to return for blood sampling	Failed to return for blood sampling
Period	Prior to Period II	Prior to Period II	Period II	Period II
Replacement	No	No	No	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Anorexia	1	0
Dizziness	1	1
Dyspepsia	0	1
Fatigue	1	1
Headache	1	4
Total:	**4**	**7**

Comments: *(on adverse events)*

Treatment-related adverse events were generally mild and comparable between the test and reference drug products. The events did not compromise the study integrity.

Table 4 Protocol Deviations

Four subjects (#1, #2, #3 and #4) took occasional analgesics and decongestants during the study period. Seventeen (17) deviations in blood sampling (< 13-minute delays – 5 and 12 cases of "no show") were reported. Actual sampling times were used in analyses. The integrity of the study was not compromised.

Table 5 Assay Validation – Within Study

Vol. 1.2, pp. 645 - 665		
	Carbamazepine	Carbamazepine 10, 11 epoxide
QC Conc.	0.20 – 7.00 mcg/mL	0.02 – 0.70 mcg/mL
Inter day Precision (%CV)	2.6 – 7.1%	2.6 – 7.5%
Inter day Accuracy (%)	106.0 – 113.0%	105.0 – 109.0%
Cal. Standards Conc.	0.10 – 10.0 mcg/mL	0.01 – 1.00 mcg/mL
Inter day Precision (%CV)	1.5 – 5.3%	1.6 – 10.0%
Inter day Accuracy (%)	95.0 – 102.0%	98.0 – 101.0%
Linearity Range	$\geq$ 0.9989	$\geq$ 0.9998

Chromatograms: Any interfering peaks? None

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
L200.107	6/20/2001	Sample Analysis

Comments on repeat assays.

There were no pharmacokinetic repeats reported. Seventeen (17) samples ('low internal standard' – 16 and 'lab accident' – 1) were repeated. The results of the repeated runs were reported as the final results according to the pre-established SOP #L200.107.

Comments on Within-Study Validation: The within-study validation is complete.

Conclusion: Analytical method is acceptable.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 10 and Figure 1

Carbamazepine						
Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	mcg*/mL	166.85	37.88	170.23	26.94	0.98
AUC∞	mcg*/mL	184.56	29.06	179.80	25.82	1.03
Cmax	mcg/mL	1.84	33.42	1.99	20.07	0.93
Tmax	hr	28.36	35.93	24.18	34.04	1.17
T1/2	hr	41.96	17.89	41.45	18.01	1.01
kel	hr^{-1}	0.02	18.02	0.02	18.25	0.99

Carbamazepine 10, 11-epoxide						
Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	mcg*/mL	10.08	54.01	10.34	42.79	0.97
AUC∞	mcg*/mL	11.57	42.75	11.26	38.94	1.03
Cmax	mcg/mL	0.11	47.11	0.12	37.72	0.94
Tmax	hr	41.09	37.54	40.27	26.87	1.02
T1/2	hr	41.94	26.51	40.52	17.26	1.04
kel	hr^{-1}	0.02	22.81	0.02	18.90	0.99

Table 8 Least Square Geometric Means and 90% Confidence Intervals

Carbamazepine				
Parameter	Test	Reference	T/R	90% CI
AUC0-t	166.83	163.88	1.02	93.2 – 111.1
AUC∞	176.6	173.6	1.02	93.6 – 110.4
Cmax	1.88	1.95	0.96	89.5 – 103.9

Carbamazepine 10, 11-epoxide				
Parameter	**Test**	**Reference**	**T/R**	**90% CI**
AUC0-t	9.38	9.27	1.01	91.1 – 112.1
AUC∞	10.54	10.36	1.02	93.9 – 110.1
Cmax	0.11	0.11	0.98	90.0 – 106.8

Table 9 Additional Study Information

Carbamazepine		
Root mean square error, AUC0-t	0.168	
Root mean square error, AUC∞	0.158	
Root mean square error, Cmax	0.143	
mean ratio AUC0-t/AUC∞	**T** = 0.94	**R** = 0.94
Range of values, ratio AUC0-t/AUC∞	T = 0.89 – 0.97	**R** = 0.88 – 0.98

Carbamazepine 10, 11-epoxide		
Root mean square error, AUC0-t	0.198	
Root mean square error, AUC∞	0.152	
Root mean square error, Cmax	0.164	
mean ratio AUC0-t/AUC∞	**T** = 0.89	**R** = 0.90
Range of values, ratio AUC0-t/AUC∞	T = 0.71 – 0.97	**R** = 0.61 – 0.97

Comments: (on pharmacokinetic analysis)

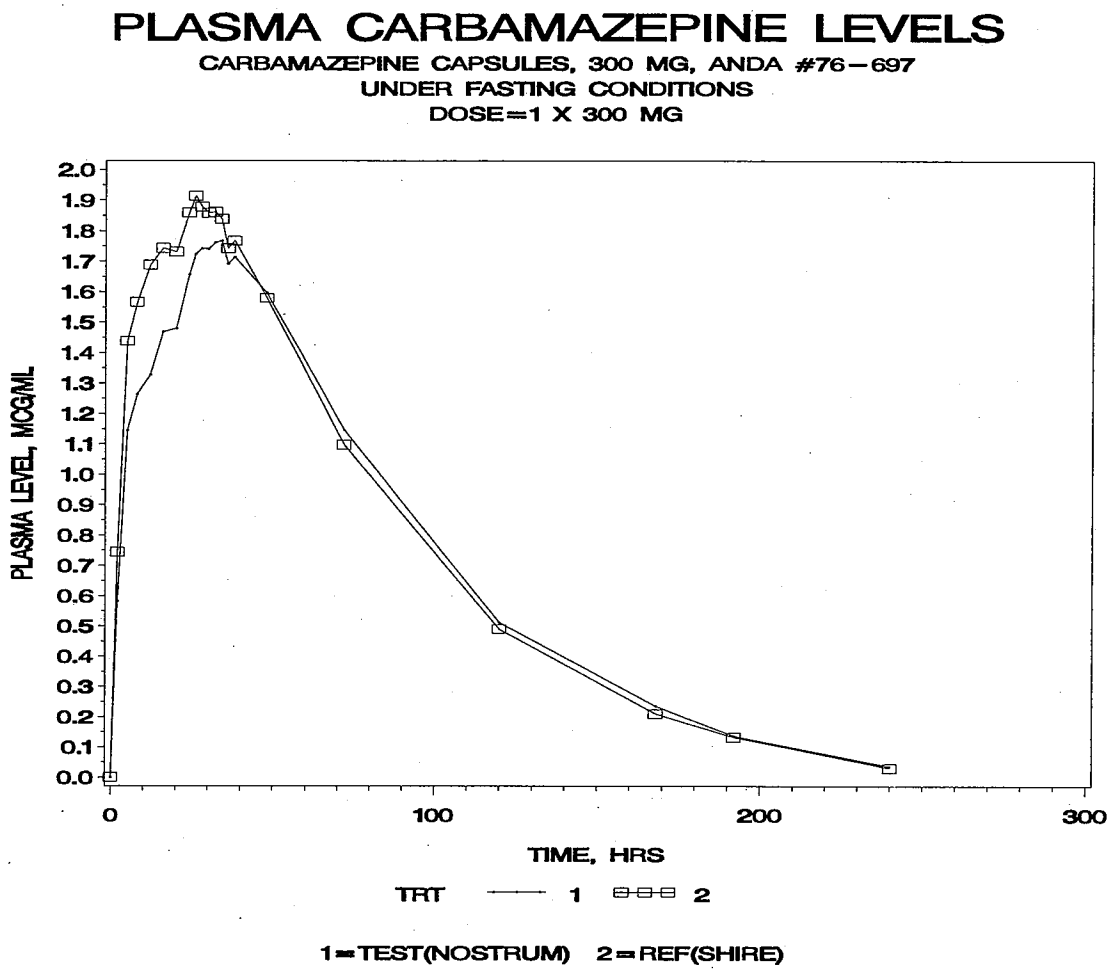
- Ke and AUCi were determined for all subjects.
- Measurable drug concentrations at 0 hr: None
- First measurable drug concentration at Cmax: None
- Were there statistically significant sequence or period effects? No
- The 90% confidence intervals are within the acceptable limits of 80-125% for the ln-transformed parameters of AUCt, AUCi, Cmax.
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.

Conclusion: The single-dose fasting bioequivalence study is acceptable.

Table 10 Mean Plasma Carbamazepine Concentrations (mcg/mL), Single-Dose Fasting Bioequivalence Study

	Test (n = 22)		Reference (n = 22)		T/R
TIME HR	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
2	0.58	52.85	0.74	30.20	0.78
5	1.15	42.17	1.44	21.08	0.80
8	1.26	37.34	1.57	18.32	0.81
12	1.33	35.02	1.69	15.80	0.79
16	1.47	32.48	1.74	18.37	0.84
20	1.48	33.52	1.73	18.53	0.85
24	1.66	33.27	1.86	20.33	0.89
26	1.72	32.61	1.91	21.88	0.90
28	1.74	33.98	1.88	21.76	0.93
30	1.74	34.60	1.86	21.97	0.94
32	1.76	34.50	1.86	23.61	0.95
34	1.77	35.23	1.84	24.13	0.96
36	1.69	36.07	1.74	25.16	0.97
38	1.71	35.64	1.77	26.13	0.97
48	1.60	37.62	1.58	27.74	1.01
72	1.15	41.40	1.10	31.13	1.04
120	0.51	44.99	0.49	35.40	1.04
168	0.24	53.25	0.21	52.03	1.12
192	0.14	85.99	0.13	76.62	1.03
240	0.04	194.30	0.03	198.52	1.18

Figure 1 Mean Plasma Carbamazepine Concentrations (mcg/mL), Single-Dose Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	PRACS R02-734
Study Title	Randomized, Single-Dose, 2-way Crossover Bioequivalence Study of Martec and Shire (Carbatrol®) 300 mg Carbamazepine ER Capsules under Non-Fasting Conditions
Clinical Site	PRACS Institute, Ltd., Fargo, North Dakota
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Period I: August 10 – 20, 2002; Period II: September 7 – 17, 2002
Analytical Site	(b) (4)
Analytical Director	(b) (6) M.S.
Analysis Dates	October 30 – November 15, 2002
Storage Period	97 days [Long-term Stability: 153 days]

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Carbamazepine ER	Carbatrol® Capsules
Manufacturer	Martec	Shire Richwood, Inc.
Batch/Lot No.	020313	GY41
Manufacture Date	3/27/2002	N/A
Expiration Date	N/A	02/03
Strength	300 mg	300 mg
Dosage Form	Capsules	Capsules
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.59% (RSD: 0.39%)	102.07% (RSD: 0.22%)
Content Uniformity	100.62% (RSD: 0.92%)	101.72% (RSD: 1.80%)
Formulation	See Appendix Section B	
Dose Administered	1 x 300 mg	
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	28 days
Randomization Scheme	AB: 2,3,4,6,8,11,13,16,18 BA: 1,5,7,9,10,12,14,15,17
Blood Sampling Times	0,2,5,8,10,12,13,14,15,16,18,24,30,36,48,72,120, 168, 192, and 240 hours
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	- 20^0 C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 11
Length of Fasting	10 hours
Length of Confinement	46 hours
Safety Monitoring	Same as Fasting Study

Table 11 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	100
Mean	23.6	Mean	77.2	18-40	100	Male	72.2	Afr. Amer.	
SD	4.5	SD	10.8	41-64		Female	27.8	Hispanic	
Range	20 – 37	Range	58.1 - 99	65-75				Asian	
				>75				Others	

Study Results

Table 12 Dropout Information

None

Table 13 Study Adverse Events

Adverse Event Description	**# in Test Group**	**# in Reference Group**
Stomachache		1
Dirrhea	1	
Dizziness		1
Dyspepsia		2
Fatigue	1	
Headache		2
Sore Throat		1
Thirsty	1	
Vomiting	1	
Total	**4**	**7**

Comments: *(on adverse events)*

Adverse events associated with the test product were less compared to the reference and mild. The events did not compromise the study integrity.

Table 14 Protocol Deviations

Three subjects (#1, #2, and #3) took vitamins within 3 days of study initiation. Eighteen (18) deviations in blood sampling (sampling delays – 14 and "no show" - 4) were reported. Actual sampling times were used in analyses. The integrity of the study was not compromised.

Table 15 Assay Validation – Within Study

Vol. 1.4, pp. 2077 - 2101		
	Carbamazepine	Carbamazepine 10, 11 epoxide
QC Conc.	0.20 – 7.00 mcg/mL	0.02 – 0.70 mcg/mL
Inter day Precision (%CV)	4.6 – 7.2%	4.8 – 10.5%
Inter day Accuracy (%)	93.0 – 102.0%	95.0 – 103.0%
Cal. Standards Conc.	0.10 – 10.0 mcg/mL	0.01 – 1.00 mcg/mL
Inter day Precision (%CV)	1.2 – 3.1%	1.3 – 5.0%
Inter day Accuracy (%)	99.0 – 101.0%	98.0 – 100.0%
Linearity Range	$\geq$ 0.9994	$\geq$ 0.9991

Chromatograms: Any interfering peaks? No

Table 16 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
L200.107	6/20/2001	Sample Analysis

Comments on repeat assays:

There were no pharmacokinetic repeats reported. Twenty-two (22) samples ('low internal standard' – 17, 'diluted sample' - 4 and 'lab accident' – 1) were repeated. The results of the repeated runs were reported as the final results according to the pre-established SOP #L200.107.

Comments on Within-Study Validation: The within-study validation is complete.

Conclusion: Analytical method is acceptable.

Table 17 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 20 and Figure 2

Carbamazepine						
Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	mcg*/mL	171.14	25.17	191.78	16.07	0.89
AUC∞	mcg*/mL	179.76	23.78	199.81	15.74	0.90
Cmax	mcg/mL	2.18	22.10	2.67	16.90	0.82
Tmax	hr	22.06	27.84	15.00	46.02	1.47
T1/2	hr	39.60	18.18	38.77	17.18	1.02
kel	hr^{-1}	0.02	20.38	0.02	19.14	0.98

Carbamazepine 10, 11-epoxide						
Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	mcg*/mL	11.24	39.25	13.10	27.35	0.86
AUC∞	mcg*/mL	12.23	33.63	13.90	25.73	0.88
Cmax	mcg/mL	0.14	34.78	0.16	29.71	0.84
Tmax	hr	39.67	18.08	34.67	20.18	1.14
T1/2	hr	36.85	23.10	35.70	15.59	1.03
kel	hr^{-1}	0.02	20.18	0.02	15.31	0.99

Table 18 Geometric Means and 90% Confidence Intervals

Carbamazepine				
Parameter	Test	Reference	T/R	90% CI
AUC0-t	165.89	189.47	0.88	80.3 – 95.4
AUC∞	174.83	197.48	0.89	81.8 – 95.8
Cmax	2.12	2.64	0.80	**74.7** – 86.7

Carbamazepine 10, 11-epoxide				
Parameter	Test	Reference	T/R	90% CI
AUC0-t	10.43	12.70	0.82	**72.3** – 93.2
AUC∞	11.62	13.52	0.86	**78.1** – 94.6
Cmax	0.13	0.16	0.83	**75.2** – 91.0

Table 19 Additional Study Information

Carbamazepine		
Root mean square error, AUC0-t	0.148	
Root mean square error, AUC∞	0.136	
Root mean square error, Cmax	0.128	
mean ratio AUC0-t/AUC∞	T = 0.95	R = 0.96
Range of values, ratio AUC0-t/AUC∞	T = 0.90 – 0.98	R = 0.92 – 0.97

Carbamazepine 10, 11-epoxide		
Root mean square error, AUC_{0-t}	0.218	
Root mean square error, AUC_{∞}	0.164	
Root mean square error, C_{max}	0.164	
mean ratio AUC_{0-t}/AUC_{∞}	T = 0.90	**R** = 0.94
Range of values, ratio AUC_{0-t}/AUC_{∞}	T = 0.65 – 0.98	**R** = 0.90 – 0.97

Comments: (on pharmacokinetic analysis)

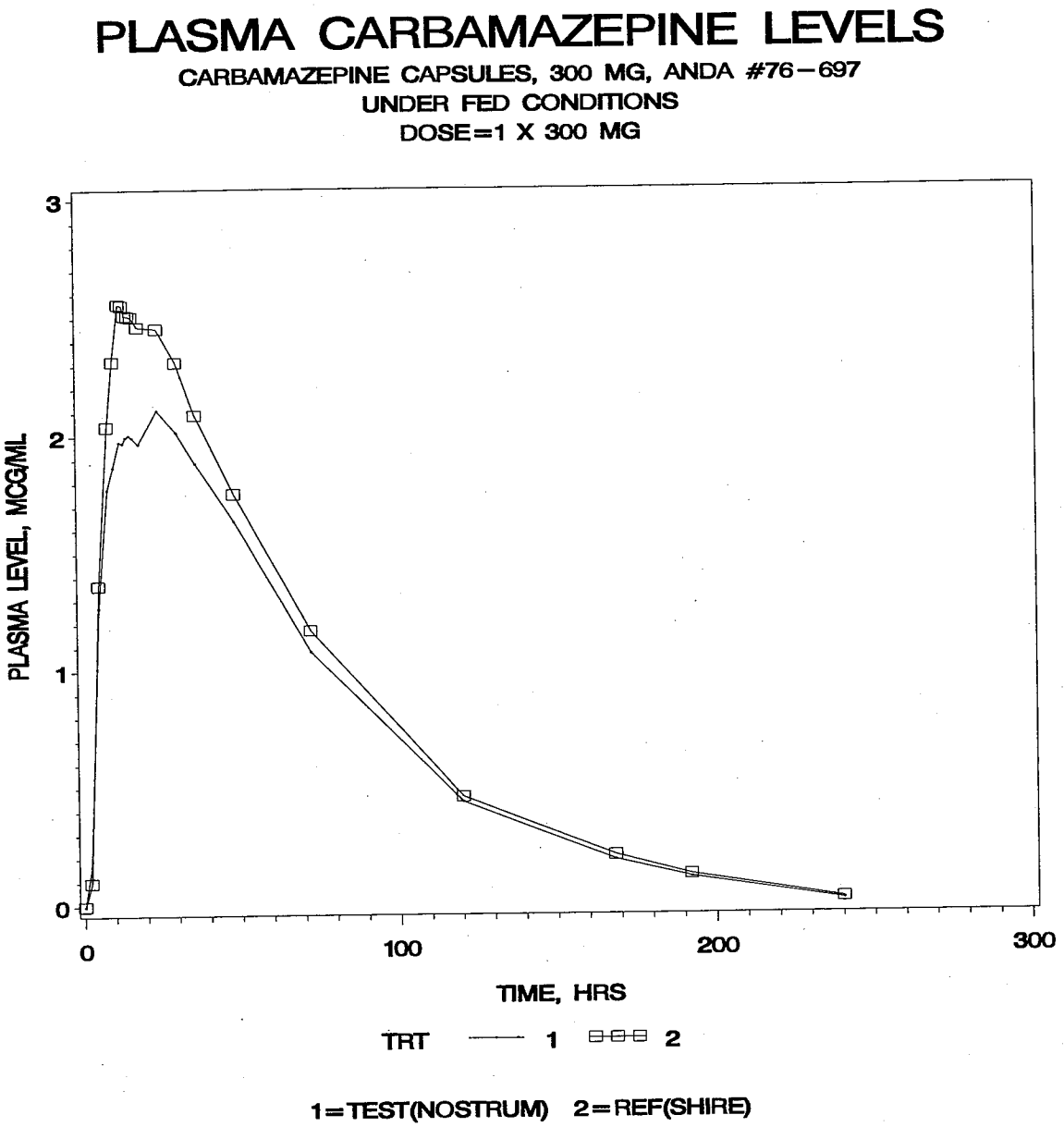
- Ke and AUCi were determined for all subjects.
- Measurable drug concentrations at 0 hr: None
- First measurable drug concentration at Cmax: None
- Were there statistically significant sequence or period effects? No
- The 90% confidence intervals are within the acceptable limits of 80-125% for the ln-transformed parameters of AUCt and AUCi. *The 90% CIs are outside the 80 – 125% limits for the Cmax of carbamazepine and all the three parameters for the epoxide metabolite. However, the study meets the acceptance criteria in place at the time it was initiated.*
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.

Conclusion: The single-dose fed bioequivalence study is acceptable.

Table 20: Mean Plasma Carbamazepine Concentrations (mcg/mL), Single-Dose Fed Bioequivalence Study

	Test (n = 18)		Reference (n = 18)		T/R
TIME HR	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00		
2	0.17	90.32	0.10	112.13	1.72
5	1.27	31.02	1.37	35.08	0.93
8	1.77	20.49	2.04	27.16	0.87
10	1.87	21.31	2.32	23.09	0.81
12	1.98	22.01	2.56	19.26	0.77
13	1.97	22.80	2.56	17.74	0.77
14	2.00	23.12	2.51	16.97	0.79
15	2.01	23.12	2.51	15.17	0.80
16	2.00	22.87	2.51	15.88	0.80
18	1.97	22.80	2.46	18.89	0.80
24	2.11	22.80	2.46	17.39	0.86
30	2.02	22.39	2.31	15.22	0.87
36	1.88	24.33	2.09	15.83	0.90
48	1.64	27.18	1.75	17.55	0.93
72	1.08	29.19	1.17	19.45	0.92
120	0.44	32.32	0.46	28.02	0.95
168	0.19	46.08	0.21	41.38	0.91
192	0.11	71.29	0.12	64.73	0.90
240	0.01	282.80	0.02	225.75	0.66

Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

Ingredient	mg/capsule	% w/w
Carbamazepine, USP	300.00	(b) (4)
(b) (4)	(b) (4)	
Sodium Lauryl Sulfate, USP		
(b) (4)		
Total Weight		

C. Dissolution Data

Table 1

Test: Carbamazepine ER Capsules				Reference: Carbatrol® Capsules		
Lot No.: 020313				Lot No.: GY41		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
Water with 1% SLS [Basket; 100 RPM]						
Time(hours)	Mean	Range	%RSD	Mean	Range	%RSD
1	42.25	(b) (4)	2.84	62.44	(b) (4)	7.53
2	60.56		3.20	85.86		4.58
4	80.27		2.05	96.63		2.73
6	89.71		2.01	97.60		3.68
8	94.42		1.76	100.52		1.92
10	97.82		1.60	99.20		1.07
12	100.95		0.96	99.17		1.32
pH 1.2 Buffer with 1% SLS [Basket; 100 RPM]						
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
1	35.52	(b) (4)	5.47			
2	52.43		4.12			
4	71.71		2.48			
6	81.49		2.40			
8	87.43		2.09			
10	90.92		1.62			
12	93.58		2.03			
pH 4.5 Buffer with 1% SLS [Basket; 100 RPM]						
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
1	38.09	(b) (4)	2.95			
2	54.77		3.52			
4	74.66		2.44			
6	85.23		1.83			
8	91.83		3.34			
10	95.31		1.78			
12	98.99		2.81			

Test: Carbamazepine ER Capsules				Reference: Carbatrol® Capsules		
Lot No.: 020313				Lot No.: GY41		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
pH 6.0 Buffer with 1% SLS [Basket; 100 RPM]						
Time(hours)	Mean	Range	%RSD	Mean	Range	%RSD
1	42.25	(b) (4)				
2	60.56					
4	80.27					
6	89.71					
8	94.42					
10	97.82					
12	100.95					
pH 7.5 Buffer with 1% SLS [Basket; 100 RPM]						
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
1	40.06	(b) (4)	3.77			
2	57.55		2.16			
4	78.39		1.61			
6	89.27		1.39			
8	96.77		1.11			
10	101.24		1.21			
12	102.86		1.06			
Water with 1% SLS [Basket; *75 RPM*]						
Time(hours)	Mean	Range	%RSD	Mean	Range	%RSD
1	37.99	(b) (4)	6.42			
2	55.75		5.78			
4	75.36		4.61			
6	85.54		3.73			
8	90.69		2.91			
10	93.91		3.18			
12	95.45		3.20			
Water with 1% SLS [Basket; *150 RPM*]						
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
1	43.31	(b) (4)	4.66			
2	60.56		2.69			
4	79.50		2.21			
6	89.45		2.71			
8	94.72		4.89			
10	97.45		1.39			
12	101.94		2.66			

Figure 3 Dissolution Profiles (*optional*)

D. Consult Reviews

None

E. SAS Output

Fasting	C:\Data\SAS\ CBZpar76697fast_	C:\Data\SAS\ CBZmet76697fast_
Non-Fasting	C:\Data\SAS\ CBZpar76697fed_	C:\Data\SAS\ CBZmet76697fed_

F. Additional Attachments

-----Original Message-----
From: Tran, Nhan L
Sent: Tuesday, January 06, 2004 1:51 PM
To: Nwakama, Patrick E
Cc: Singh, Gur J P
Subject: DISSOLUTION FOR CARBAMAZEPINE ER CAPSULES (CARBATROL)

Hi Patrick:

I do not believe that the firm has submitted adequate dissolution data for carbamazepine ER capsules. Hence I suggest that the following items should be added to your list of deficiencies:

1. Conduct COMPARATIVE dissolution testing of the test and reference products using USP Apparatus I (Basket) at 100 RPM in 900 ml water, pH 1.2, 4.5 and 6.8 with AND without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs. The use of higher SLS concentration should be justified and fully documented.

2. Conduct COMPARATIVE dissolution testing of the test and reference products using USP Apparatus II (Paddle) at 50 RPM and 75 RPM in 900 ml water, pH 1.2, 4.5 and 6.8 with AND without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs. The use of higher SLS concentration should be justified and fully documented.

3. In addition, the firm is suggested to use the following FDA recommended dissolution method:

USP Apparatus II (Paddle) at 75 RPM
Medium: 900 ml of dissolution media
First 4 hrs: pH 1.1 HCl
After 4 hrs: pH 7.5 phosphate buffer with 0.1% SLS

Sampling times: 1, 4, 6 and 12 hrs.

Please remember, those are only my suggestions. Please discuss with your TL for his concurrence.

Thanks for asking,

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-697 APPLICANT: Nostrum Pharmaceuticals, Inc

DRUG PRODUCT: Carbamazepine ER Capsules, 300 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. Please submit a bioequivalence study in which the test and reference products are administered by sprinkling the capsule contents over a spoonful of applesauce. Subjects should be fasted overnight before receiving the study drugs in applesauce. The sprinkle study is requested to support the relevant labeling of this product. Bioequivalence assessment will be based on carbamazepine data.

2. Please conduct comparative dissolution testing of the test and reference products using:

   a) USP Apparatus I (Basket) at 100 rpm in 900 ml water, pH 1.2, 4.5 and 6.8 with and without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs.

   b) USP Apparatus II (Paddle) at 50 rpm and 75 rpm in 900 ml water, pH 1.2, 4.5 and 6.8 with and without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs.

   c) In addition, please use the following dissolution method:

      USP Apparatus II (Paddle) at 75 RPM
      Medium: 900 ml of dissolution media
      First 4 hrs: pH 1.1 HCl
      After 4 hrs: pH 7.5 phosphate buffer with 0.1% SLS
      Sampling times: 1, 4, 6 and 12 hrs

The use of higher SLS concentration should be justified and fully documented.

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA 76-697
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama

V:\FIRMSNZ\Nostrum\LTRS&REV\76-697S0303.doc
Printed in final on 1/29/2004

Endorsements: (Final with Dates)
HFD-658/ P.Nwakama 1/29/2004
HFD-658/ GJP Singh 1/29/04
HFD-650/ S.Mazzella
HFD-650/ D. Conner 1/29/04

BIOEQUIVALENCY - Incomplete Submission Date: 01/21/2003

1. **FASTING STUDY** (STF) Strengths: 300 mg
Clinical: PRACS Institute, Fargo **Outcome: IC**
Analytical: (b) (4)

2. **FOOD STUDY** (STP) Strength: 300 mg
Clinical: PRACS Institute, Fargo **Outcome: IC**
Analytical: (b) (4)

Outcome Decisions: IC - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-697
Drug Product Name	Carbamazepine Extended Release Capsules
Strength	300 mg
Applicant Name	Nostrum Pharmaceuticals, Inc.; c/o Martec Pharmaceutical, Inc.
Address	1800 N. Topping, Kansas City, MO 64120
Submission Date(s)	October 5, 2004
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsNZ \ Nostrum\ltrs&rev\76697a1004.doc

I. Executive Summary

This is a review of a study amendment. Nostrum Pharmaceuticals previously submitted fasting and non-fasting bioequivalence (BE) studies on its Carbamazepine ER Capsules, 300 mg. Statistical analyses of the plasma concentration data for carbamazepine and carbamazepine 10, 11-epoxide in both studies demonstrated bioequivalence. The two BE studies were acceptable but the application was incomplete because the additional fasting (Sprinkle) BE study was not conducted and the dissolution testing was not performed according to the FDA-recommended method and specifications.

In this amendment, the firm has submitted the results of the sprinkle fasting study conducted in healthy adult males and females (n = 27). Carbamazepine results were (point estimate, 90% CI): LAUCT of 0.87, 81.98 – 92.37%; LAUCI 0.88, 82.72 – 93.20%; and LCmax 0.85, 80.34 – 90.60%. Statistical analysis of carbamazepine PK data demonstrates bioequivalence while the analysis of carbamazepine 10, 11-epoxide by the firm does not pass BE criteria. In the original DBE deficiency letter (2/3/2004), the firm was informed that bioequivalence assessment will be based on carbamazepine parent data.

The application is incomplete. The firm's proposed dissolution method and specifications are not acceptable. The DBE has recommended specifications based on the newly submitted data. The firm should acknowledge its acceptance of the FDA's recommended dissolution method and specifications [900 mL, pH 1.2 buffer (with 0.1% SLS), Apparatus I (Basket); 100 rpm and specifications - 1 hr: (b) (4)%, 4 hr: (b) (4)%, 8 hr: (b) (4) (b) (4)%, 12 hr: NLT(b) (4)%].

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Carbamazepine ER Capsules, 300 mg
Reference Product	Carbatrol® XL Capsules, 300 mg
RLD Manufacturer	Shire Pharmaceutics
NDA No.	20712
RLD Approval Date	September 30, 1997
Indication	Anticonvulsant and treatment of trigeminal neuralgia

B. PK/PD Information

(V:\firmsNZ \ Nostrum\ltrs&rev\76697n0303.doc)

Study Amendment:

Deficiency Comment #1:

Please submit a bioequivalence study in which the test and reference products are administered by sprinkling the capsule contents over a spoonful of applesauce. Subjects should be fasted overnight before receiving the study drugs in applesauce. The sprinkle study is requested to support the relevant labeling of this product. Bioequivalence assessment will be based on carbamazepine data.

FIRM'S RESPONSE:
The required study has been conducted and bioequivalence was assessed on the basis of the carbamazepine data as stated in the FDA's deficiency letter. The firm used a new RLD lot because of the expiration of the original biolot.

Deficiency Comment #2:
Please conduct comparative dissolution testing of the test and reference products using:

a) USP Apparatus I (Basket) at 100 rpm in 900 ml water, pH 1.2, 4.5 and 6.8 with and without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs.

b) USP Apparatus II (Paddle) at 50 rpm and 75 rpm in 900 ml water, pH 1.2, 4.5 and 6.8 with and without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs.

c) In addition, please use the following dissolution method:

USP Apparatus II (Paddle) at 75 RPM
Medium: 900 ml of dissolution media
First 4 hrs: pH 1.1 HCl
After 4 hrs: pH 7.5 phosphate buffer with 0.1% SLS
Sampling times: 1, 4, 6 and 12 hrs

FIRM'S RESPONSE:
The dissolution testing was conducted at (b) (4)
The firm plans to update the CMC section of the original ANDA to include this analytical laboratory in its subsequent FDA amendment submission. The company information (including its GMP statement) and the test methodology have been included in this submission. In the drug profile report, capsules exhibiting (b) (4) capsule data. The firm plans to address this issue of (b) (4) in a pending CMC manufacturing amendment.

Deficiency Comment #3:
The use of higher SLS concentration should be justified and fully documented.

FIRM'S RESPONSE:
The submitted dissolution data support the use of SLS in various media using Basket at 100 rpm. The criteria used to develop appropriate dissolution method and specifications were based on generation of comparable dissolution profiles and specification of NLT (b) (4)% (Q) at 12-hour sampling point. A significant dissolution data on this ANDA and ongoing stability testing support the use of the originally proposed dissolution method (900 mL, Water w/1% SLS, Baskets at 100 rpm) and specifications (1 hr: NMT (b) (4)%, 4 hr: (b) (4)%, 12 hr: NLT (b) (4)%).

The dissolution testing conducted by (b) (4) in response to this deficiency letter along with the historical data provided in the original submission, provide justification for adoption of the use of the dissolution method (900 mL, Water w/1% SLS, Baskets at 100 rpm). Dissolution testing conducted without SLS show that SLS is needed for adequate drug release (> (b) (4)% in 12 h). The concentration of SLS (1% vs. 0.1% SLS) is important since several dissolution conditions using lower SLS failed to produce adequate drug release.

Dissolution profiles meeting the adequate drug release criteria ((b) (4)% in 12 h) were obtained with two dissolution methods (pH 1.2 w/ 0.1% SLS, Paddle at 75 rpm; pH 1.2 w/ 0.1% SLS, Basket at 100 rpm). However, the use of pH 1.2 media is not appropriate for an ER product which is not likely to dissolve completely in the low acidic pH of the stomach but, rather, in the intestinal tract with higher pH. The use of Basket (vs. Paddle) generally reduces the variability associated with capsule floating and capsule movement in and out of the vortex. The data on the dissolution media containing 0.1% SLS demonstrates minimal compliance with (b) (4)% (Q) specification at L2 (failing at L1). The firm believes that a higher level SLS (1%) is needed for release and stability testing to allow for routine batch to batch variability and normal analytical test variability and that the use of a lower level of SLS (0.1%) would be too stringent for routine use. Therefore, the firm still insists in keeping its originally proposed dissolution method [900 mL, Water (w/1% SLS), Basket at 100 rpm.

Relevant OGD or DBE History	No controlled documents, protocols or ANDAs have previously been submitted for carbamazepine ER capsules. Two ANDAs (# (b) (4) and # (b) (4)) have been submitted for carbamazepine ER tablets and ANDA # (b) (4) has been found acceptable by the DBE.
Agency Guidance	CDER 2002 BA/BE guidance
Drug Specific Issues	The NDA (bioequivalence) study included the determination of carbamazepine as well as its active metabolite carbamazepine epoxide. A sprinkle fasting study was also conducted.

C. Contents of Submission

Study Types	Yes/No?	How many?
Applesauce Sprinkling	Yes	1
In vitro dissolution	Yes	1
Amendments	Yes	1

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D. Pre-Study Bioanalytical Method Validation

Vol. 1.1, pp. 437 - 475		
	Parent	**Metabolite**
Analyte name	**Carbamazepine**	**Carbamazepine 10, 11-Epoxide**
Internal Standard	(b) (4)	(b) (4)
Method description	LC/MS/MS	LC/MS/MS
QC range	0.20 to 7.00 mcg/mL	0.02 to 0.70 mcg/mL
Standard curve range	0.10 to 10.00 mcg/mL	0.01 to 1.00 mcg/mL
Limit of quantitation	0.10 mcg/mL	0.01 mcg/mL
Average recovery of Drug (%)	79.0%	49.9%
Average Recovery of Int. Std (%)	91.9%	91.9%
Intraday precision range (%CV)	0.8 to 3.7%	1.6 to 5.6%
Intraday accuracy range (%)	92.5 to 102.0%	90.0 to 103.0%
Intraday precision range (%CV)	1.2 to 3.4%	3.3 to 5.3%
Intraday accuracy range (%)	95.5 to 101%	95.0 to 100.0%
Interday precision range (%CV)[STD]	1.0 to 4.2%	1.1 to 10.0%
Interday accuracy range (%)[STD]	96.0 to 104.0%	98.0 to 104.0%
Bench-top stability (hrs)	24 hours	24 hours
Stock stability (days)	66 days	66 days
Processed stability (hrs)	72 hours	72 hours
Freeze-thaw stability (cycles)	3 cycles	3 cycles
Long-term storage stability (days)	153 day	153 days
Dilution integrity	2 to 4-fold, 107 to 101%	2 to 4-fold, 110.0 to 102%
Specificity	Yes	Yes
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes
20% Chromatograms included (Y/N)	Yes	Yes
Random Selection of Serial Chrom	Yes	Yes

NOTE: This is the same information as submitted in the original submission (3/26/2003).

E. In Vivo Studies

1. Single-dose Fasting (Sprinkle) Bioequivalence Study

Study Summary	
Study No.	10482801
Study Design	Randomized, Single-Dose, 2-way Crossover, Relative Bioavailability Study
No. of subjects enrolled	28
No. of subjects completing	27 (Subject #24 withdrew prior to Period II)
No. of subjects analyzed	27
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 11 Female: 16
Test product	Carbamazepine ER Capsules
Reference product	Carbatrol® Capsules
Strength tested	300 mg
Dose	1 x 300 mg

Summary of Statistical Analysis Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
Carbamazepine		
AUC0-t	0.87	81.98 – 92.37
AUC∞	0.88	82.72 – 93.20
Cmax	0.85	80.34 – 90.60
Carbamazepine 10, 11-epoxide		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	0.87	80.10 – 95.34
AUC∞	0.85	78.95 – 90.74
Cmax	0.83	76.19 – 90.51

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic Repeats	0	0	0	0	0	0	0	0
Laboratory Accident	0	1	0	0.07	0	1	0	0.07
Low Internal Standard	1	0	0.07	0	1	0	0.07	0
Sample Not Injected	16	16	1.1	1.1	16	16	1.1	1.1
Unacceptable Chromatography	2	0	0.14	0	2	0	0.14	0
Total	**19**	**17**	**1.31**	**1.17**	**19**	**17**	**1.31**	**1.17**

Total Number of Samples – 1454

Did use of recalculated plasma concentration data change study outcome? N/A

Comments on Sprinkle Fasting Study: Acceptable.

F. Formulation

Location in appendix	Section B, Page 22
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored? (yes or no)	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	N/A

NOTE: This is the same formulation as submitted in the original submission dated 3/26/2003.

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA-recommended Methods
Medium	various media (see Table 12)
Volume (mL)	900 mL
USP Apparatus type	Apparatus I (Basket) and II (Paddle)
Rotation (rpm)	50, 75, and 100 rpm
Firm's proposed specifications	N/A
FDA-recommended specifications	N/A
F2 metric calculated (yes or no)	N/A
If no, reason why F2 not calculated	Single strength
Method is acceptable (yes or no)	Yes

F2 metric, other strengths compared to biostudy strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A (single strength)			

F2 metric, test compared to reference	
Strength	F2 metric
N/A (multiple dissolution methods)	

H. Waiver Request(s)

Strengths for which waivers requested	None
Regulation cited	N/A
Proportional to strength tested in vivo (yes or no)	N/A
Dissolution is acceptable (yes or no)	Yes (DBE has recommended specifications)
Waiver granted (yes or no)	N/A

I. Comments

The firm has submitted pharmacokinetic data on carbamazepine and carbamazepine 10, 11-epoxide in the fasting sprinkle study. The parent drug passes BE statistics while the LAUCI and LCmax of carbamazepine epoxide do not demonstrate BE of the test product to the RLD. Statistical analyses of both carbamazepine and carbamazepine epoxide data in the previous fasting and fed BE studies demonstrated bioequivalence. In its deficiency letter (2/3/04), the DBE informed the firm that *Bioequivalence assessment will be based on carbamazepine data.*

J. Recommendations

1. The single-dose, fasting and fed bioequivalence studies conducted by Nostrum Pharmaceuticals on its product, Carbamazepine ER Capsules, 300 mg, lot # 020313, comparing it with the reference product, Shire Richwood's Carbatrol® XL Capsules, 300 mg, lot # GY41, are acceptable. The test product, Nostrum's Carbamazepine ER Capsules, 300 mg, is deemed bioequivalent to the reference product, Shire Richwood's Carbatrol® XL Capsules, 300 mg, under both fasting and fed conditions.

2. The single-dose, sprinkle fasting bioequivalence study conducted by Nostrum Pharmaceuticals on its Carbamazepine ER Capsules, 300 mg, lot # 020313, comparing it with the reference product, Shire Richwood's Carbatrol® XL Capsules, 300 mg, lot # 3C2470, is acceptable. The test product, Nostrum's Carbamazepine ER Capsules, 300 mg, is deemed bioequivalent to the reference product, Shire Richwood's Carbatrol® XL Capsules, 300 mg, under sprinkle, fasting conditions.

3. The dissolution testing should be conducted in 900 mL, pH 1.2 buffer (with 0.1% SLS) using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following FDA recommended specifications:

1 hr:	(b) (4)%
4 hr:	%
8 hr:	%
12 hr:	NLT (b) (4)%

From bioequivalence point of view, the application is incomplete. The firm should acknowledge acceptance of the FDA-recommended dissolution method and specifications.

Patrick Nwakama, Pharm.D.	Team III	11/16/04 Date signed
Yih-Chain Huang, Ph.D.	Team III	11/16/2004 Date signed
Dale P. Conner, Pharm. D. Director, Division of Bioequivalence Office of Generic Drugs		11/16/04

IV. Appendix

A. Individual Study Reviews

1. Single-dose Sprinkle Fasting Bioequivalence Study

Study Information	
Study Number	10482801
Study Title	Relative Bioavailability Sprinkle Study of Carbamazepine 300 mg ER Capsules under Fasting Conditions
Clinical Site	Novum Pharmaceutical Research Services, Houston, Texas
Principal Investigator	So Ran Hong, M.D.
Study/Dosing Dates	Period I: March 23, 2004; Period II: April 20, 2004
Analytical Site	(b) (4)
Analytical Director	(b) (6) M.S.
Analysis Dates	March 23 – June 8, 2004
Storage Period	77 days [Long-term Stability: 153 days]

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Carbamazepine ER	Carbatrol® Capsules
Manufacturer	Martec	Shire Richwood, Inc.
Batch/Lot No.	020313	3C2470
Manufacture Date	3/27/2002	N/A
Expiration Date	N/A	02/03
Strength	300 mg	300 mg
Dosage Form	Capsules	Capsules
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	100.59% (RSD: 0.39%)	102.38% (RSD: 1.83%)
Content Uniformity	100.62% (RSD: 0.92%)	101.76% (RSD: 0.82%)
Formulation	See Appendix Section B	
Dose Administered	1 x 300 mg	1 x 300 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	28 days
Randomization Scheme	AB: 1,3,5,8,9,12,14,15,17,19,21,24,25,28 BA: 2,4,6,7,10,11,13,16,18,20,22,23,26,27
Blood Sampling Times	0.5,1,2,3,4,5,6,8,10,12,15,20,24,26,28,30,32,34,36,38, 48,72,120, 168,192, and 240 hours
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	- 20^0 C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours
Length of Confinement	48 hours
Safety Monitoring	Subjects were monitored throughout the confinement portion of the study. Vital signs were taken prior to dosing and as scheduled post-dosing.

Table 1 Demographics of Study Subjects (n = 27)

Age		Weight (lb)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	0.00
Mean	35.9	Mean	190.9	18-40	63.0	Male	40.7	Afr. Amer.	77.8
SD	10.9	SD	34.4	41-64	37.0	Female	59.3	Hispanic	18.5
Range	19 – 55	Range	125 – 260	65-75				Asian	
				>75				Others	3.7

Study Results

Table 2 Dropout Information

Subject No	Subject #24
Reason	Withdrew for personal reasons
Period	Prior to Period II
Replacement	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Drowsiness	2	2
Dizziness	0	1
Total:	**2**	**3**

Comments: (*on adverse events)*

Treatment-related adverse events were generally mild and comparable between the test and reference drug products. The events did not compromise the study integrity.

Table 4 Protocol Deviations

Fifty seven (57) deviations in blood sampling (< 1 hr delays – 49; 1 – 3 h – 4; and 4 cases of "no show") were reported. Actual sampling times were used in analyses. The integrity of the study was not compromised.

Table 5 Assay Validation – Within Study

Vol. 1.1, pp. 496 - 525		
	Carbamazepine	**Carbamazepine 10, 11 epoxide**
QC Conc.	0.20 – 7.00 mcg/mL	0.02 – 0.70 mcg/mL
Inter day Precision (%CV)	3.2 – 4.7%	3.9 – 5.7%
Inter day Accuracy (%)	99.8 – 105.0%	97.0 – 102.0%
Cal. Standards Conc.	0.10 – 10.0 mcg/mL	0.01 – 1.00 mcg/mL
Inter day Precision (%CV)	1.1 – 3.8%	1.5 – 5.2%
Inter day Accuracy (%)	98.7 – 102.0%	97.2 – 105.0%
Linearity Range	$\geq$ 0.9995	$\geq$ 0.9989

Chromatograms: Any interfering peaks? None

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
L200.107	6/20/2001	Sample Analysis

Comments on repeat assays.

There were no pharmacokinetic repeats reported. Thirty-six (36) samples ('low internal standard' – 1, 'laboratory accident' – 1, 'sample not injected' - 32 and 'unacceptable chromatography' – 2) were repeated. The results of the repeated runs were reported as the final results according to the pre-established SOP #L200.108.

Comments on Within-Study Validation: The within-study validation is complete.

Conclusion: Analytical method is acceptable.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 10 and Table 11 Mean Plasma **Carbamazepine 10, 11-Epoxide Concentrations (mcg/mL), Single-Dose Sprinkle Fasting Bioequivalence Study**

	Test (n = 27)		Reference (n = 27)		T/R
TIME (hour)	Mean Conc.	% CV	Mean Conc.	% CV	
0	0.00	.	0.00	.	.
0.5	0.00	.	0.00	.	.
1	0.00	.	0.00	191.85	0.00
2	0.01	127.01	0.02	54.58	0.34
3	0.01	68.50	0.03	35.39	0.51
4	0.02	46.30	0.03	37.20	0.60
5	0.03	34.28	0.04	37.29	0.65
6	0.03	33.33	0.04	34.98	0.66
8	0.03	36.27	0.05	35.04	0.70
10	0.04	32.89	0.05	35.23	0.68
12	0.04	36.73	0.06	33.76	0.71
15	0.05	32.80	0.07	32.96	0.72
20	0.05	33.49	0.07	31.44	0.73
24	0.06	33.36	0.09	29.89	0.76
26	0.07	31.45	0.09	27.19	0.75
28	0.07	31.01	0.09	29.16	0.77
30	0.08	30.48	0.09	27.25	0.80
32	0.08	33.71	0.10	29.58	0.81

	Test (n = 27)		Reference (n = 27)		
34	0.08	34.40	0.10	30.19	0.79
36	0.08	31.79	0.10	27.81	0.81
38	0.08	32.34	0.10	26.94	0.80
48	0.09	37.18	0.10	31.86	0.88
72	0.08	40.24	0.09	33.85	0.91
120	0.04	40.96	0.05	36.57	0.88
168	0.02	59.59	0.02	62.63	0.94
192	0.01	80.85	0.01	77.78	0.89
240	0.00	156.72	0.01	127.60	0.83

Figure 1 and Figure 2

Carbamazepine						
Parameter	**Units**	**Test**		**Reference**		**T/R**
		Mean	**%CV**	**Mean**	**% CV**	
AUC0-t	mcg*/mL	202.41	29.52	230.63	26.24	0.88
AUC∞	mcg*/mL	216.89	29.92	245.37	27.29	0.88
Cmax	mcg/mL	1.99	22.26	2.31	17.60	0.86
Tmax	hr	34.89	34.88	25.30	32.41	1.38
T1/2	hr	52.71	28.32	52.16	23.34	1.01
Kel	hr^{-1}	0.01	27.47	0.01	25.10	1.01

Carbamazepine 10, 11-epoxide						
Parameter	**Units**	**Test**		**Reference**		**T/R**
		Mean	**%CV**	**Mean**	**% CV**	
AUC0-t	mcg*/mL	9.70	35.27	11.15	34.08	0.87
AUC∞	mcg*/mL	10.91	32.03	12.54	27.85	0.87
Cmax	mcg/mL	0.09	34.07	0.11	27.57	0.85
Tmax	hr	48.15	29.71	46.81	34.53	1.03
T1/2	hr	53.16	40.52	48.94	23.33	1.09
Kel	hr^{-1}	0.01	29.10	0.01	21.12	0.97

Table 8 Least Squares Geometric Means and 90% Confidence Intervals

Carbamazepine				
Parameter	**Test**	**Reference**	**T/R**	**90% CI**
AUC0-t	193.94	222.88	0.87	81.98 – 92.37
AUC∞	207.83	236.71	0.88	82.72 – 93.20
Cmax	1.94	2.27	0.85	80.34 – 90.60

Carbamazepine 10, 11-epoxide				
Parameter	**Test**	**Reference**	**T/R**	**90% CI**
AUC0-t	9.07	10.37	0.87	80.10 – 95.34
AUC∞	10.29	12.16	0.85	**78.95** – 90.74
Cmax	0.09	0.10	0.83	**76.19** – 90.51

Table 9 Additional Study Information

Carbamazepine		
Root mean square error, AUC0-t	0.1283	
Root mean square error, AUC∞	0.1281	
Root mean square error, Cmax	0.1292	
mean ratio AUC0-t/AUC∞	**T** = 0.93	**R** = 0.94
Range of values, ratio AUC0-t/AUC∞	**T** = 0.85 – 0.97	**R** = 0.88 – 0.97

Carbamazepine 10, 11-epoxide		
Root mean square error, AUC0-t	0.1871	
Root mean square error, AUC∞	0.1408	
Root mean square error, Cmax	0.1851	
mean ratio AUC0-t/AUC∞	**T** = 0.89	**R** = 0.89
Range of values, ratio AUC0-t/AUC∞	**T** = 0.65 – 0.96	**R** = 0.64 – 0.96

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for all subjects.
- Measurable drug concentrations at 0 hr: None
- First measurable drug concentration at Cmax: None
- Were there statistically significant sequence or period effects? No
- The 90% confidence intervals for carbamazepine are within the acceptable limits of 80-125% for the LAUCT, LAUCI, LCmax. The 90% CIs for carbamazepine 10, 11-epoxide for LAUCI and LCmax are outside the acceptable limits.
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.

Conclusion: The single-dose sprinkle fasting bioequivalence study is acceptable since the firm was originally informed that bioequivalence will be based on assessment of carbamazepine data.

Table 10 Mean Plasma Carbamazepine Concentrations (mcg/mL), Single-Dose Sprinkle Fasting Bioequivalence Study

	Test (n = 27)		Reference (n = 27)		T/R
TIME (hour)	Mean Conc.	% CV	Mean Conc.	% CV	
0	0.00	.	0.00	.	.
0.5	0.05	148.95	0.21	45.04	0.23
1	0.30	40.51	0.62	35.93	0.48
2	0.56	30.23	1.04	28.48	0.54
3	0.80	27.14	1.35	25.84	0.59
4	0.96	23.25	1.55	25.19	0.62
5	1.10	23.18	1.64	24.71	0.67
6	1.19	23.24	1.71	21.87	0.70
8	1.28	25.36	1.79	21.96	0.71
10	1.35	25.38	1.85	20.02	0.73
12	1.41	26.27	1.89	19.27	0.74
15	1.54	22.84	2.02	19.15	0.76
20	1.59	22.60	2.05	18.58	0.78
24	1.75	22.86	2.15	19.62	0.82
26	1.84	22.61	2.23	19.76	0.83
28	1.88	23.07	2.21	19.03	0.85
30	1.89	23.98	2.17	18.84	0.87
32	1.82	24.11	2.06	21.53	0.88
34	1.81	25.54	2.10	20.18	0.86
36	1.80	25.39	2.03	20.77	0.89
38	1.83	25.29	2.06	21.11	0.89
48	1.79	28.72	1.91	25.74	0.93
72	1.35	34.31	1.47	29.40	0.92
120	0.70	40.48	0.76	38.13	0.91
168	0.36	52.88	0.40	49.96	0.92
192	0.25	67.50	0.28	57.93	0.89
240	0.13	88.27	0.15	82.04	0.92

Table 11 Mean Plasma Carbamazepine 10, 11-Epoxide Concentrations (mcg/mL), Single-Dose Sprinkle Fasting Bioequivalence Study

	Test (n = 27)		Reference (n = 27)		T/R
TIME (hour)	Mean Conc.	% CV	Mean Conc.	% CV	
0	0.00	.	0.00	.	.
0.5	0.00	.	0.00	.	.
1	0.00	.	0.00	191.85	0.00
2	0.01	127.01	0.02	54.58	0.34
3	0.01	68.50	0.03	35.39	0.51
4	0.02	46.30	0.03	37.20	0.60
5	0.03	34.28	0.04	37.29	0.65
6	0.03	33.33	0.04	34.98	0.66
8	0.03	36.27	0.05	35.04	0.70
10	0.04	32.89	0.05	35.23	0.68
12	0.04	36.73	0.06	33.76	0.71
15	0.05	32.80	0.07	32.96	0.72
20	0.05	33.49	0.07	31.44	0.73
24	0.06	33.36	0.09	29.89	0.76
26	0.07	31.45	0.09	27.19	0.75
28	0.07	31.01	0.09	29.16	0.77
30	0.08	30.48	0.09	27.25	0.80
32	0.08	33.71	0.10	29.58	0.81
34	0.08	34.40	0.10	30.19	0.79
36	0.08	31.79	0.10	27.81	0.81
38	0.08	32.34	0.10	26.94	0.80
48	0.09	37.18	0.10	31.86	0.88
72	0.08	40.24	0.09	33.85	0.91
120	0.04	40.96	0.05	36.57	0.88
168	0.02	59.59	0.02	62.63	0.94
192	0.01	80.85	0.01	77.78	0.89
240	0.00	156.72	0.01	127.60	0.83

Figure 1 Mean Plasma Carbamazepine Concentrations (mcg/mL), Single-Dose Sprinkle Fasting Bioequivalence Study

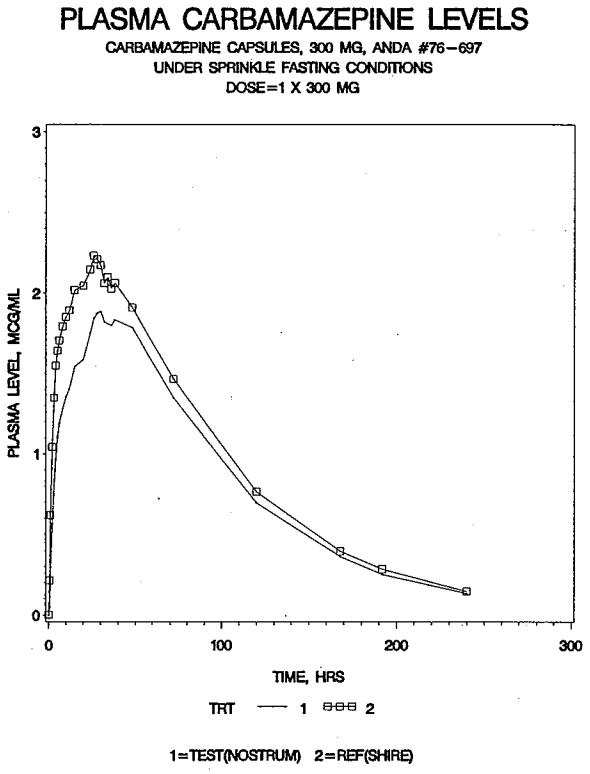
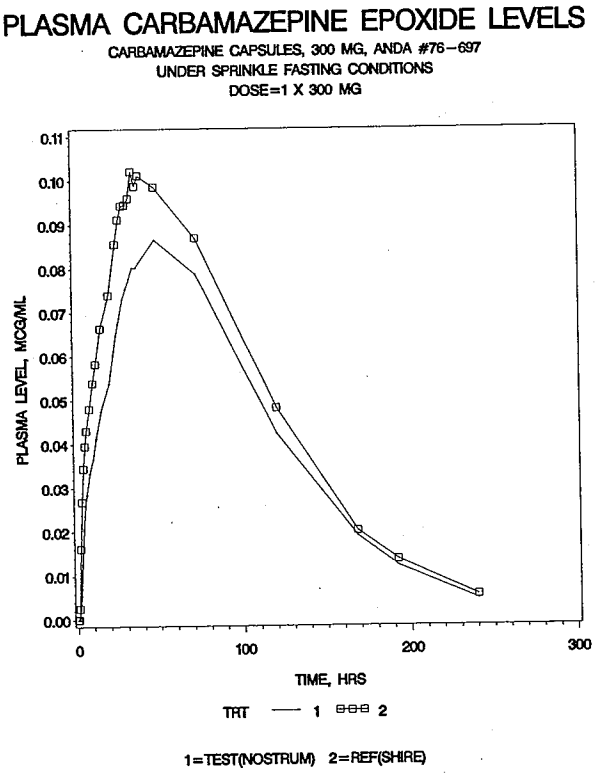


Figure 2 Mean Plasma Carbamazepine 10, 11 – Epoxide Concentrations (mcg/mL), Single-Dose Sprinkle Fasting Bioequivalence Study



B. Formulation Data

Ingredient	mg/capsule	%w/w
Carbamazepine, USP	300.00	(b) (4)
(b) (4)	(b) (4)	
Sodium Lauryl Sulfate, USP		
(b) (4)		
(b) (4)		
Total Weight		100.00

C. Dissolution Data

Table 12

Test: Carbamazepine ER Capsules				Reference: Carbatrol® Capsules		
Lot No.: 020313				Lot No.: 3C2470		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
Water [Paddle; 50 RPM]						
Time(hours)	Mean	Range	%RSD	Mean	Range	%RSD
1	10.62	(b) (4)	11.1	12.38	(b) (4)	19.5
2	17.94		8.6	18.99		17.1
4	28.25		7.4	27.62		11.9
6	36.01		5.4	34.75		9.3
8	42.03		5.0	37.53		8.9
10	46.38		4.3	40.50		6.9
12	49.56		4.7	42.82		7.3
Water [Paddle; 75 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	20.19	(b) (4)	5.3	23.27	(b) (4)	5.6
2	30.31		5.3	32.29		4.8
4	44.56		5.4	42.80		3.9
6	54.59		4.2	49.39		2.5
8	60.18		3.9	52.20		2.7
10	64.82		3.0	54.79		2.1
12	69.17		3.4	56.86		2.1
Water [Basket; 100 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	20.08	(b) (4)	3.4	16.14	(b) (4)	3.7
2	30.65		2.3	25.68		2.8
4	44.10		1.9	36.74		2.2
6	53.57		2.8	42.10		2.0
8	62.05		4.2	46.51		1.9
10	65.53		3.9	50.44		2.4
12	69.98		2.1	53.24		1.2

Test: Carbamazepine ER Capsules				Reference: Carbatrol® Capsules		
Lot No.: 020313				Lot No.: 3C2470		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
pH 1.2 [Paddle; 50 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	11.45	(b) (4)	7.0	11.85	(b) (4)	10.6
2	20.98		10.6	19.06		11.2
4	31.26		5.9	27.10		8.7
6	38.81		6.9	33.92		8.9
8	43.93		4.3	37.81		7.3
10	49.58		4.1	40.69		8.1
12	52.89		4.5	42.77		6.7
pH 1.2 [Paddle; 75 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	18.48	(b) (4)	9.1	17.93	(b) (4)	6.4
2	28.36		4.8	29.88		8.2
4	42.14		5.6	41.09		3.1
6	50.89		4.8	48.94		3.4
8	57.57		3.8	52.19		2.1
10	63.13		2.9	56.94		2.9
12	66.20		3.2	57.59		2.9
pH 1.2 [Basket; 100 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	19.09	(b) (4)	2.4	14.62	(b) (4)	4.5
2	29.96		2.8	23.26		3.8
4	46.67		2.8	34.55		2.6
6	55.84		2.3	39.08		2.4
8	59.75		1.2	42.33		2.1
10	65.49		3.1	45.69		3.1
12	69.61		3.8	46.98		3.7

Test: Carbamazepine ER Capsules	Reference: Carbatrol® Capsules
Lot No.: 020313	Lot No.: 3C2470
Strength: 300 mg	Strength: 300 mg
No. of Units: 12	No. of Units: 12

pH 4.5 [Paddle; 50 RPM]

Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	10.28	(b) (4)	6.9	14.99	(b) (4)	7.4
2	17.61		5.2	19.94		9.5
4	28.33		3.3	29.09		8.3
6	35.83		3.0	35.40		8.1
8	42.17		3.2	38.68		7.5
10	47.30		2.7	41.72		7.3
12	51.36		3.1	43.48		6.5

pH 4.5 [Paddle; 75 RPM]

Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	18.95	(b) (4)	4.3	21.81	(b) (4)	10.6
2	30.83		1.9	32.96		7.6
4	43.66		2.2	43.29		6.2
6	52.60		2.6	52.41		7.6
8	58.48		2.3	54.72		4.8
10	61.78		1.6	56.02		4.6
12	66.82		4.4	58.60		3.7

pH 4.5 [Basket; 100 RPM]

Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	21.13	(b) (4)	8.4	16.17	(b) (4)	6.7
2	30.99		8.2	21.39		6.3
4	45.60		3.1	33.07		4.0
6	54.46		2.2	40.55		3.7
8	61.15		2.8	44.31		3.8
10	66.43		2.6	48.00		2.9
12	71.22		1.9	50.54		2.7

Test: Carbamazepine ER Capsules				Reference: Carbatrol® Capsules		
Lot No.: 020313				Lot No.: 3C2470		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
pH 6.8 Buffer [Paddle; 50 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	11.20	(b) (4)	6.1	14.05	(b) (4)	9.7
2	19.26		6.8	22.04		8.3
4	30.23		6.7	31.59		8.7
6	37.40		4.4	36.38		8.7
8	43.62		4.3	39.67		9.4
10	48.79		4.0	43.79		9.7
12	53.69		4.2	45.97		8.8
pH 6.8 Buffer [Paddle; 75 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	16.80	(b) (4)	6.0	25.14	(b) (4)	7.0
2	27.04		8.9	38.29		4.8
4	41.02		4.8	52.06		4.2
6	49.78		2.9	59.98		2.8
8	56.37		4.2	60.43		2.7
10	63.32		4.4	64.47		2.9
12	70.65		9.3	63.70		3.8
pH 6.8 Buffer [Basket; 100 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	17.99	(b) (4)	5.7	18.61	(b) (4)	4.4
2	26.95		7.8	29.29		3.7
4	44.83		4.6	42.62		2.2
6	53.20		3.9	49.43		1.8
8	60.68		4.7	53.50		2.3
10	64.29		4.4	56.84		2.4
12	65.48		3.5	58.13		2.6

Test: Carbamazepine ER Capsules				Reference: Carbatrol® Capsules		
Lot No.: 020313				Lot No.: 3C2470		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
Water (w/ 0.1% SLS) [Paddle; 50 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	11.92	(b) (4)	6.7	11.71	(b) (4)	5.0
2	20.19		4.1	16.49		7.0
4	32.98		3.7	26.34		6.9
6	41.19		3.2	36.22		7.8
8	45.90		2.8	39.53		7.9
10	49.24		6.5	44.23		7.1
12	52.41		4.3	48.30		7.3
Water (w/ 0.1% SLS) [Paddle; 75 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	21.00	(b) (4)	5.3	20.52	(b) (4)	9.8
2	34.57		5.0	34.59		8.3
4	48.63		4.1	52.16		5.2
6	56.72		3.3	61.42		4.0
8	59.91		2.2	66.45		2.1
10	62.62		3.0	67.48		2.8
12	63.31		2.1	69.01		3.2
Water (w/ 0.1% SLS) [Basket; 100 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	22.81	(b) (4)	5.2	14.84	(b) (4)	5.2
2	34.19		5.1	24.50		3.6
4	48.69		3.5	41.73		5.1
6	58.19		2.7	49.95		3.6
8	62.51		5.6	55.04		3.8
10	62.19		2.6	58.54		4.2
12	64.91		3.1	61.28		4.2

Test: Carbamazepine ER Capsules	Reference: Carbatrol® Capsules
Lot No.: 020313	Lot No.: 3C2470
Strength: 300 mg	Strength: 300 mg
No. of Units: 12	No. of Units: 12

pH 1.2 (w/ 0.1% SLS Buffer) [Paddle; 50 RPM]

Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	25.85	(b) (4)	4.7	25.58	(b) (4)	5.7
2	35.59		4.6	35.79		5.7
4	47.96		4.8	46.81		7.4
6	54.78		6.0	54.48		6.8
8	61.18		7.2	61.47		7.5
10	69.00		5.7	67.18		7.4
12	68.79		6.2	69.02		7.7

pH 1.2 (w/ 0.1% SLS Buffer) [Paddle; 75 RPM]

Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	36.87	(b) (4)	13.5	37.78	(b) (4)	8.1
2	47.82		6.2	58.06		6.8
4	61.30		2.9	76.39		4.6
6	70.75		5.3	84.88		4.3
8	76.33		5.6	91.27		4.0
10	82.34		6.2	93.12		5.9
12	83.57		3.9	95.25		2.6

pH 1.2 (w/ 0.1% SLS Buffer) [Basket; 100 RPM]

Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	34.55	(b) (4)	4.8	32.22	(b) (4)	2.7
2	46.48		3.5	48.14		1.9
4	60.57		3.6	65.97		2.4
6	71.21		3.3	73.86		2.9
8	78.70		3.9	78.47		3.4
10	83.66		3.3	81.62		4.0
12	85.71		3.2	83.21		3.7

Test: Carbamazepine ER Capsules	Reference: Carbatrol® Capsules
Lot No.: 020313	Lot No.: 3C2470
Strength: 300 mg	Strength: 300 mg
No. of Units: 12	No. of Units: 12

pH 4.5 (w/ 0.1% SLS Buffer) [Paddle; 50 RPM]

Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	12.66	(b) (4)	17.4	14.69	(b) (4)	8.4
2	21.80		16.6	21.84		7.7
4	35.45		14.7	29.79		8.7
6	42.22		14.4	37.43		11.8
8	53.65		14.8	45.65		12.5
10	57.88		10.6	50.21		10.0
12	64.94		9.1	57.11		10.8

pH 4.5 (w/ 0.1% SLS Buffer) [Paddle; 75 RPM]

Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	21.87	(b) (4)	9.1	30.50	(b) (4)	9.9
2	34.31		6.7	49.61		8.1
4	48.50		5.0	70.18		5.8
6	60.39		4.1	80.80		4.3
8	67.44		3.4	86.23		2.9
10	74.59		2.2	90.13		2.8
12	79.15		2.9	93.34		3.0

pH 4.5 (w/ 0.1% SLS Buffer) [Basket; 100 RPM]

Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	26.21	(b) (4)	4.9	23.82	(b) (4)	6.0
2	40.10		2.9	38.96		5.3
4	56.61		4.4	56.63		3.5
6	65.13		4.2	64.27		3.2
8	72.79		6.8	70.04		4.4
10	77.93		2.6	74.10		4.9
12	82.90		1.8	78.50		5.4

Test: Carbamazepine ER Capsules				Reference: Carbatrol® Capsules		
Lot No.: 020313				Lot No.: 3C2470		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
pH 6.8 (w/ 0.1% SLS Buffer) [Paddle; 50 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	12.50	(b) (4)	20.7	13.70	(b) (4)	27.6
2	25.69		8.2	23.75		9.1
4	36.48		11.6	34.81		10.7
6	46.60		11.0	44.05		11.3
8	54.79		10.5	51.35		11.4
10	62.87		8.0	56.64		10.8
12	66.11		9.8	62.06		10.3
pH 6.8 (w/ 0.1% SLS Buffer) [Paddle; 75 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	18.63	(b) (4)	13.4	31.58	(b) (4)	8.3
2	30.38		13.5	50.21		6.8
4	43.91		12.1	67.90		5.7
6	54.34		11.0	76.51		4.8
8	60.79		11.3	81.32		2.5
10	66.04		9.9	85.50		3.4
12	69.89		11.8	87.02		2.2
pH 6.8 (w/ 0.1% SLS Buffer) [Basket; 100 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	20.61	(b) (4)	10.2	22.69	(b) (4)	2.2
2	32.48		8.9	37.81		14.8
4	46.56		9.8	55.17		5.5
6	55.89		10.7	63.30		4.8
8	62.86		10.7	67.03		5.2
10	68.53		10.8	70.42		3.7
12	73.03		9.8	71.68		5.0

Test: Carbamazepine ER Capsules				Reference: Carbatrol® Capsules		
Lot No.: 020313				Lot No.: 3C2470		
Strength: 300 mg				Strength: 300 mg		
No. of Units: 12				No. of Units: 12		
pH 1.1 and pH 7.5 (w/ 0.1% SLS) [Paddle; 75 RPM]						
Time (hour)	Mean	Range	%RSD	Mean	Range	%RSD
1	20.87	(b) (4)	6.4	20.84	(b) (4)	7.0
4	44.19		4.6	42.01		3.3
6	58.14		3.7	73.94		3.3
12	82.57		2.7	95.86		1.6

D. Consult Reviews

-----Original Message-----
From: Tran, Nhan L
Sent: Tuesday, October 26, 2004 10:36 AM
To: Nwakama, Patrick E
Subject: RE: Dissolution Consult - ANDA 76697 (Carbamazepine ER Capsules)

For carbamazepine, the firm has done a lot of work, and I think we have enough information on the performance of the dosage form as far as in-vitro testing is concerned. I have reviewed all data submitted, and the following recommendation on the method and tolerances are made based on drug release profile, and variability. The method which gives the most discriminating profile and the least variable (%CV) is selected as follows:

For carbamazepine ER capsules:

Apparatus: USP Apparatus I (Basket)
Speed: 100 RPM
Medium: pH 1.2 w 0.1% SLS, 900 ml
Tolerances:
1 hr: (b) (4)%
4 hr: %
8 hr: %
12 hr: NLT (b) (4)%

Hope this will help,

E. SAS Output

	Carbamazepine	Carbamazepine 10, 11-epoxide
SAS PROGRAM	 76697CBZfastprog.txt	 76697CBZFASTmetprog.txt
SAS DATA	 76697CBZFAST.xls	 76697CBZmetabFAST.xls
SAS OUTPUT	 76697CBZFAST_output.txt	 76697CBZmetabFAST_output.txt

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-697 APPLICANT: Nostrum Pharmaceuticals, Inc

DRUG PRODUCT: Carbamazepine ER Capsules, 300 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Your proposed dissolution method and specifications are not acceptable. Your dissolution data are acceptable. However, please acknowledge that you have accepted the following dissolution method and specifications:

The dissolution testing should be conducted in 900 mL of pH 1.2 buffer with 0.1% SLS using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following FDA recommended specifications:

1 hr	(b) (4) %
4 hr	%
8 hr	%
12hr	NLT (b) (4)

Sincerely yours,

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA 76-697
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama

V:\FIRMSNZ\Nostrum\LTRS&REV\76697a1004.doc
Printed in final on 11/16/2004

Endorsements: (Final with Dates)
HFD-658/ P.Nwakama PE 11/16/2004
HFD-658/ YC Huang YH 11/16/2004
HFD-650/ S.Mazzella
HFD-650/ D. Conner DBR 11/16/04

BIOEQUIVALENCE - Incomplete Submission Date: October 5, 2004

1. **FASTING (Sprinkle) STUDY** (STF) oil Strengths: 300 mg
Clinical:Novum Research Services, Houston, Tx **Outcome: IC**
Analytical: (b) (4)

Outcome Decisions: IC - Incomplete

JAN 11 2005

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76697 SPONSOR: Nostrum Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM: Carbamazepine ER Capsules
STRENGTH(S): 300 mg

TYPES OF STUDIES: Fasting, Fasting (Sprinkle) and Fed Studies
CLINICAL STUDY SITE(S): Novum Pharmaceutical Research Services (Sprinkle); PRAC Institute Ltd (Fasting and Fed)
ANALYTICAL SITE(S): (b) (4)

STUDY SUMMARY: see review

DISSOLUTION: FDA-recommended method (with different specifications).

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic _Yes__ New facility _____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes_____ No__X____
(If No, Project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Spec acknowledged by firm: Yes _Date 30 DEC 04_____

PROJECT MANAGER: _Steven Mazzella_____ DATE:__7 JAN 05_____

PRIMARY REVIEWER: Patrick Nwakama, Pharm.D. BRANCH: III

INITIAL: _____ DATE: 1/11/05

TEAM LEADER: Yih-Chain Huang, Ph.D. BRANCH: III

INITIAL: _____ DATE: 1/11/2005

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: _____ DATE: 1/11/05

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76697		
Drug Product Name	Carbamazepine Extended Release Capsules		
Strength(s)	100 mg, 200 mg and 300 mg		
Applicant Name	Nostrum Pharmaceuticals Inc.		
Address	505 Thornall Street, Edison, NJ 08837		
Applicant's Point of Contact	Dhiren N. Shah, Ph.D., RAC		
Contact's Telephone Number	(816) 308-4970		
Contact's Fax Number	(816) 841-4634		
Original Submission Date(s)	March 26, 2003		
Submission Date(s) of Amendment(s) Under Review	April 28, 2008		
Reviewer	Patrick E. Nwakama, Pharm.D.		
Study Number (s)	0710050	0712061	0712062
Study Type (s)	Fasting	Fed	Fasting Sprinkle
Strength (s)	1 x 300 mg	1 x 300 mg	1 x 300 mg
Clinical Site	RelClin, Reliance Clinical Pharmacology and Pharmacokinetic Facility		
Clinical Site Address	Rabale, Navi Mumbai, India		
Analytical Site	(b) (4)		
Analytical Site Address			
OUTCOME DECISION	**INCOMPLETE**		

1 EXECUTIVE SUMMARY

In the original application (March 26, 2003), Nostrum Pharmaceuticals previously submitted fasting and non-fasting bioequivalence (BE) studies on its Carbamazepine ER Capsules, 300 mg. Statistical analyses of the plasma concentration data for carbamazepine and carbamazepine 10, 11-epoxide in both studies demonstrated bioequivalence. The two BE studies were acceptable but the application was incomplete because the additional fasting (Sprinkle) BE study was not conducted and the dissolution testing was not performed according to the FDA-recommended method and specifications. In the original amendment (October 5, 2004), the firm submitted the results of the sprinkle fasting study. Although the statistical analysis of carbamazepine pharmacokinetic data demonstrated bioequivalence, the analysis of the active metabolite, carbamazepine 10, 11-epoxide, by the firm did not pass BE criteria. The FDA found the BE studies acceptable based on the results of parent drug alone. However, the application was found incomplete pending the firm's acknowledgement of the FDA's recommended dissolution method and specifications [900 mL, pH 1.2 buffer (with 0.1%

SLS), Apparatus I (Basket); 100 rpm and specifications - 1 hr: (b) (4)%, 4 hr: (b) (4)%, 8 hr: (b) (4)%, 12 hr: NLT (b) (4)%].

Following a series of communication between the OGD and the firm, OGD Chemistry sent a Major deficiency letter informing the firm that their original biobatch has been rendered unsuitable for in vivo bioequivalence studies due to (b) (4)

In the current submission, the firm has submitted results of three new BE (fasting, fed and fasting sprinkle) studies comparing Nostrum Pharmaceuticals Carbamazepine Extended Release Capsules, 300 mg to the corresponding reference product, Shire's Carbatrol® Extended Release Capsules, 300mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects.

The firm's fasting, fed and fasting (sprinkle) BE studies are acceptable based on the parent drug carbamazepine. The results are summarized in the tables below.

Carbamazepine 300 mg
Fasting Bioequivalence Study No. 0710050, N= 22*
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

	carbamazepine				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	209938.0	222505.0	0.94	87.66	101.56
AUC∞ (ng·hr/mL)	224511.8	239890.9	0.94	87.23	100.41
Cmax (ng/mL)	2172.50	2262.23	0.96	88.63	104.06

* Subject No. 1 was excluded from PK analysis by the reviewer because of vomiting within the 12-hour dosing interval.

Carbamazepine 300 mg
Fed Bioequivalence Study No. 0710061, N= 22
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

	carbamazepine				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	203184.1	227368.7	0.89	82.59	96.69
AUC∞ (ng·hr/mL)	222576.3	240932.7	0.92	87.55	97.48
Cmax (ng/mL)	2395.60	2644.59	0.91	86.75	94.58

Carbamazepine 300 mg
Fasting Sprinkle Bioequivalence Study No. 0710062, N= 24
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

	carbamazepine				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	153180.1	168673.0	0.91	85.36	96.62
AUC∞ (ng·hr/mL)	161477.4	177183.9	0.91	85.57	97.07
Cmax (ng/mL)	1667.70	1896.23	0.88	82.72	93.51

In all three BE studies, the parent drug, carbamazepine, met the 90% CI acceptance criteria for AUCT, AUCI and Cmax. Therefore, all the BE studies are acceptable.

The firm has conducted comparative dissolution testing on all strengths using its own method. The dissolution results are not acceptable. The firm should repeat dissolution testing using the FDA-recommended dissolution method for this drug product as posted on the external website for all three strengths and in three additional pH media for the highest strength, 300 mg, per CDER 2003 BA/BE Guidance for modified release drug products.

There are no DSI inspections pending for this application.

The application is incomplete.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Carbamazepine Extended Release Capsules, 100 mg, 200 mg and 300 mg
Reference Product	Carbatrol® XL Capsules, 300 mg (also available in 100 mg and 200 mg strengths)
RLD Manufacturer	Shire Pharmaceuticals
NDA No.	20-712
RLD Approval Date	09/30/1997
Indication	Anticonvulsant therapy and treatment of pain associated with trigeminal neuralgia.

3.2 PK/PD Information

Bioavailability	Approximately 85%. Pharmacokinetics are linear over a single dose range of 200 – 800 mg extended release.
Food Effect	Tmax decreased (24 hours to 14 hours) and Cmax increased (3.2 - 4.3 mcg/mL) when a single 400 mg dose was administered with a high fat meal. The AUC was not affected by food. Based on the RLD labeling, the pharmacokinetic profile of ER carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.
Tmax	19 hours (single-dose 200 mg ER capsule); 5.9 (chronic administration of 800 mg every 12 hours)
Metabolism	The metabolic fate of carbamazepine has not been completely elucidated. A major metabolic pathway appears to be oxidation by microsomal enzymes in the liver (principally cytochrome P-450 3A4) to form carbamazepine 10,11-epoxide (CBZ-E), which is almost completely metabolized to *trans*-10,11-dihydroxy-10,11-dihydrocarbamazepine (*trans*-CBZ-diol) and excreted in urine mainly unconjugated.
Excretion	Excreted renally (72% unconjugated and about 3% unchanged) and the remainder is excreted fecally
Half-life	Plasma half-life generally ranges from 25-65 hours initially and from 12-17 hours with multiple dosing.
Drug Specific Issues (if any)	• The NDA (bioequivalence) study included the determination of carbamazepine as well as its active metabolite carbamazepine epoxide. • The drug should not be given to pregnant women.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	3, fasting, fed and fasting sprinkle

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	300 mg
	Subjects:	Normal healthy males and females, general population

	Additional Comments:	The submission included plasma concentrations and PK data for the active metabolite, carbamazepine 10,11-epoxide in addition to the parent drug. However, only the parent drug will be considered for purposes of establishing bioequivalence.

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	300 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	See Additional Comments under Fasting Study.

3.	**Type of study:**	Sprinkle
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	300 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	See Additional Comments under Fasting Study.

Analytes to measure (in plasma):	Carbamazepine
Bioequivalence based on:	90% CI
Waiver request of in-vivo testing:	100 mg and 200 mg
Source of most recent recommendations:	OGD #061084, (b) (4)

Summary of OGD or DBE History (for details, see Appendix 4.4):	OGD provides the following comments: 1. The following studies are recommended to establish bioequivalence of carbamazepine extended-release capsules: a. A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Carbamazepine Extended-release Capsules, 300 mg, to the reference listed drug (RLD), Carbatrol® (Carbamazepine) Extended-release Capsules, 300 mg. b. A single-dose, two-way crossover fed *in-vivo* bioequivalence study comparing Carbamazepine Extended-release Capsules, 300 mg, to the RLD. c. A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Carbamazepine Extended-release Capsules, 300 mg, to the RLD, sprinkled on a spoonful of applesauce. 2. Please measure only the parent compound, carbamazepine. 3. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 phosphate buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve capsules. In addition, please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA method: Apparatus: USP apparatus II (paddle) Speed: 75 rpm Volume: 900 mL Medium: First 4 hours: dilute acid, pH 1.1 (the media is then removed), After 4 hours: phosphate buffer, pH 7.5, containing 0.1% sodium lauryl sulfate (SLS) Volume: 900 mL Sampling times: 1, 4, 6, and 12 hours and until at least 80% of the labeled content is dissolved. 4. Carbamazepine Extended-release Capsules, 100 mg and 200 mg, may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 300 mg strength, (2) acceptable dissolution testing of the 100 mg, 200 mg, and 300 mg strengths, and (3) proportional similarity in the formulations of the 100 mg, 200 mg, and 300 mg strengths. 5. Female subjects should not be enrolled in bioequivalence studies of carbamazepine if they are pregnant.

OGD HISTORY ON ANDA No. 76-697

March 26, 2003 (Division of Bioequivalence Review):
Original ANDA was submitted containing fasting and fed bioequivalence (BE) studies on its Carbamazepine ER Capsules, 300 mg and waiver requests for the lower strengths (100 mg and 200 mg). Statistical analyses of the plasma concentration data for carbamazepine and carbamazepine 10, 11-epoxide in both studies demonstrated bioequivalence. The two BE studies were acceptable but the application was incomplete because the additional fasting (Sprinkle) BE study was not conducted and the dissolution testing was not performed according to the FDA-recommended method and specifications.

October 5, 2004 (Division of Bioequivalence Review):
The original amendment was submitted containing the results of the sprinkle fasting study. Statistical analysis of carbamazepine PK data demonstrates bioequivalence while the analysis of carbamazepine 10, 11-epoxide by the firm does not pass BE criteria. The FDA found the BE studies acceptable based on the results of parent drug alone. However, the application was found incomplete pending the firm's acknowledgement of the FDA's recommended dissolution method and specifications [900 mL, pH 1.2 buffer (with 0.1% SLS), Apparatus I (Basket); 100 rpm and specifications - 1 hr: (b) (4)%, 4 hr: (b) (4)%, 8 hr: (b) (4)%, 12 hr: NLT (b) (4)%].

FDA Deficiency Letter (June 27, 2005) [Chemistry deficiencies presented below represent MAJOR deficiencies].

(b) (4)

The firm should contact Division of Bioequivalence for any additional bioequivalence requirements due to the manufacturing concerns raised.

FDA Deficiency Letter (May 1, 2006) [Chemistry deficiencies presented below represent MAJOR deficiencies].

The Office of Generic Drugs uses data generated on the pivotal batch not only to demonstrate bioequivalence to the Reference Listed Drug, but also as a quality benchmark. Because of the importance of this batch, it is essential that details of its manufacture be unassailable. Since the manufacture of the test exhibit batch, the firm has agreed to the addition of critical drug product manufacturing process controls, including control of (b) (4)

Therefore, the firm was requested to manufacture a new test batch and contact the Division of Bioequivalence for *in vivo* bioequivalence study requirements. The firm was also advised that the adequacy of their manufacturing process controls would be further evaluated upon review of the new exhibit batch. Chemistry also recommended that the root cause(s) of the (b) (4) problem be determined as well as identification of appropriate corrective measures in your next amendment.

FDA Deficiency Letter (August 13, 2007) [Chemistry deficiencies presented below represent MAJOR deficiencies].

Please be aware that the Office of Generic Drugs uses data generated on the ANDA pivotal batch not only to demonstrate bioequivalence to the Reference Listed Drug, but also as a quality benchmark. Because of the importance of this batch, it is essential that details of its manufacture be unassailable. Chemistry acknowledges the changes and emphasis placed in the (b) (4)

As mentioned in previous communications, ***the apparent*** (b) (4) ***renders the original bioequivalence batch as inappropriate for in-vivo bioequivalence studies.*** We reiterate our previous request for submission of a new bioequivalence study as delineated in our last deficiency letter. The firm was asked to contact the Division of Bioequivalence for the appropriate *in vivo* bioequivalence study requirements.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Single-dose fasting (sprinkle)	Yes	1
In vitro dissolution	Yes	3
Waiver requests	Yes	2
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Carbamazepine
Analyte	Carbamazepine
Internal standard (IS)	(b) (4)
Method description	LC-MS/MS
Limit of quantitation	9.963 ng/mL
% recovery (and %CV) at each concentration tested	80.90-91.56%
Average recovery of IS (%)	85.99%
Standard curve concentrations (ng/mL)	9.963, 19.926, 99.630, 348.706, 1394.824, 2988.908, 4483.362, 5230.589, 6974.119 ng/mL
QC concentrations (ng/mL)	9.963 30.045 3129.680 5508.236 6974.119 ng/mL
QC Intraday precision range (%)	1.77 to 9.92%
QC Intraday accuracy range (%)	88.81 to 99.28%
QC Interday precision range (%)	4.15 to 7.88%
QC Interday accuracy range (%)	97.09 to 101.44
Bench-top stability (hrs)	7 1/2 hours
Stock stability (days)	10 days
Processed stability (hrs)	49 hours
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	129 days @ – 20^{0}C
Dilution integrity @ 1402.097 and 2804.192 ng/mL(CBZ); 39.719 and 79.438 ng/mL (CBZ 10,11 epoxide) (dilution factor 1/10th and 1/5th)	100.09 – 105.67% (CV: 2.42 – 2.52%)

Selectivity	Yes

SOPs submitted	Yes
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation: Acceptable

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies (Not provided by firm)

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Carbamazepine 300 mg **Fasting Bioequivalence Study No. 0710050, N= 22*** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
	carbamazepine				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	209938.0	222505.0	0.94	87.66	101.56
AUC∞ (ng·hr/mL)	224511.8	239890.9	0.94	87.23	100.41
Cmax (ng/mL)	2172.50	2262.23	0.96	88.63	104.06

*Subject No. 1 was excluded from PK analysis by the reviewer because of vomiting within the 12-hour dosing interval.

Carbamazepine 300 mg **Fed Bioequivalence Study No. 0710061, N= 22** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
	carbamazepine				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	203184.1	227368.7	0.89	82.59	96.69
AUC∞ (ng·hr/mL)	222576.3	240932.7	0.92	87.55	97.48
Cmax (ng/mL)	2395.60	2644.59	0.91	86.75	94.58

Carbamazepine 300 mg **Fasting Sprinkle Bioequivalence Study No. 0710062, N= 24** **Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals**					
	carbamazepine				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	153180.1	168673.0	0.91	85.36	96.62
AUC∞ (ng·hr/mL)	161477.4	177183.9	0.91	85.57	97.07
Cmax (ng/mL)	1667.70	1896.23	0.88	82.72	93.51

Table 3. Reanalysis of Study Samples

Fasting Study, Study No. 0710050 Additional information in Volume(s), Page(s)								
	Carbamazepine							
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
No reassays reported								

Total No. of Samples Analyzed = 1087

Fed Study, Study No. 0712061 Additional information in Volume(s), Page(s)								
	Carbamazepine							
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0	0	0	0	0	0
Unacceptable Internal Standard Response	3	1	0.33	0.11	3	1	0.33	0.11
Repeat due to processing error	0	1	0.00	0.11	0	1	0.00	0.11
Total	3	2	0.33	0.22	3	2	0.33	0.22

Total No. of Samples Analyzed = 910

Fasting (Sprinkle) Study, Study No. 0712062 Additional information in Volume(s), Page(s)								
	Carbamazepine							
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0	0	0	0	0	0
Unacceptable Internal Standard Response	10	6	0.88	0.53	10	6	0.88	0.53
Total	10	6	0.88	0.53	10	6	0.88	0.53

Total No. of Samples Analyzed = 1139

Did use of recalculated plasma concentration data change study outcome? No. No PK repeats

Comments from the Reviewer: Acceptable

3.7 Formulation

Location in appendix	Section 4.2, Page 42
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	Acceptable
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	N/A
Source of Method (USP, FDA or Firm)	Firm
Medium	0.1% SLS, pH 1.2 buffer
Volume (mL)	900 mL
USP Apparatus type	Paddle
Rotation (rpm)	100 rpm
DBE-recommended specifications	N/A
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Firm did not use FDA method
Is method acceptable?	**No**
If not then why?	Firm did not conduct dissolution testing using FDA dissolution method on the Agency's external website for all 3 strenghts and in three additional dissolution media for the 300 mg.

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
N/A			

3.9 Waiver Request(s)

Strengths for which waivers are requested	100 mg and 200 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	No
If not then why?	Firm did not conduct dissolution testing using FDA dissolution method on the Agency's external website for all 3 strengths and in three additional dissolution media for the 300 mg.

3.10 Deficiency Comments

1. The firm did not conduct dissolution testing using the FDA method posted on the external dissolution website for all three strengths and in three additional media for the highest strength (300 mg) as stated in the CDER BA/BE Guidance for modified release drug products (b) (4).

3.11 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (0710050) conducted by Nostrum on its Carbamazepine ER capsules, 300 mg (Lot # G070068B) comparing it to Shire's Carbatrol® 300 mg Capsules (lot #6N2897).

2. The Division of Bioequivalence accepts the fed BE study (0712061) conducted by Nostrum on its Carbamazepine ER capsules, 300 mg (Lot # G070068B) comparing it to Shire's Carbatrol® 300 mg Capsules (lot #6N2897).

3. The Division of Bioequivalence accepts the sprinkle BE study (0712062) conducted by the Nostrum on its Carbamazepine ER capsules, 300 mg (Lot # G070068B) comparing it to Shire's Carbatrol® 300 mg Capsules (lot #6N2897).

4. The dissolution testing conducted is incomplete. The firm should conduct dissolution testing using the FDA-recommended dissolution method posted on the FDA external website for all three strengths and in three additional media for the highest strength, 300 mg.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	0710050
Study Title	A randomized, two-treatment, two-period, two-sequence crossover comparative bioavailability study in male subjects under fasting conditions.
Clinical Site (Name & Address)	RelClin, Reliance Clinical Pharmacology and Pharmacokinetic Facility, Mumbai – 400701, India
Principal Investigator	Prashant Pandya, Ph.D.
Dosing Dates	Period I: 10/23/02; Period II: 11/13/07
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	11/28/07 to 12/04/07
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	42 days

Table 5. Product information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Carbamazepine 300 mg ER Capsules	Carbatrol® 300 mg capsules
Manufacturer	Nostrum Pharmaceuticals Inc.	Shire Richwood Inc.
Batch/Lot No.	B070068B	6N2897
Manufacture Date	09/2007	
Expiration Date		10/ 2008
Strength	300 mg	300 mg
Dosage Form	Capsule	Capsule
Bio-Batch Size	(b) (4)	
Production Batch Size		

Potency (Assay)	102.1%	N/A
Content Uniformity (mean, %CV)	101.5%	
Dose Administered	1 x 300 mg	1 x 300 mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	24 (+ 2 stand-by)*
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	AB: 2,3,5,8,10,11,13,15,17,19,21,24,26 BA:1,4,6,7,9,12,14,16,18,20,22,23,25
Blood Sampling Times	(0.0 hour) 2.0, 5.0, 8.0, 12.0, 16.0, 18.0, 20.0, 22.0, 24.0, 26.0, 28.0, 30.0, 32.0, 34.0, 36.0, 38.0, 48.0, 72.0, 120.0, 168.0, 192.0 and 240.0 hours
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	- 70^0C $\pm$ 15^0C
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	10 hours
Length of Confinement	At least 12 hours prior to dosing and until 48-hour sample collection
Safety Monitoring	Vital signs were recorded on check-in day, prior to drug administration and 4.0, 9.0 12.0, 24.0, 36.0, 48.0 (check out), 72.0, 120.0, 168.0, 192.0, and 240.0 hours after drug administration.

* Per protocol, 24 subjects were analyzed. However, subject number 7 was excluded from PK analysis because the subject showed BLQ or zero concentration in period II. Per BA/BE Guidance, Subject No. 1 was excluded from PK analysis by the reviewer because of vomiting within the 12-hour dosing interval.

Comments on Study Design: Acceptable

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. 0710050			
		Treatment Groups	
		Test Product N = 26	Reference Product N = 26
Age (years)	Mean ± SD	26 ± 5.45	26 ± 5.45
	Range	18 - 39	18 - 39
Age Groups	< 18	0(%)	0(%)
	18 – 40	26(100%)	26(100%)
	41 – 64	0(%)	0(%)
	65 – 75	0(%)	0(%)
	> 75	0(%)	0(%)
Sex	Male	26 (100%)	26 (100%)
	Female	0(0%)	0(0%)
Race	Asian	26 (100%)	26 (100%)
	Black	0(%)	0(%)
	Caucasian	0(%)	0(%)
	Hispanic	0(%)	0(%)
	Other	0(%)	0(%)
BMI	Mean + SD	21.58 ± 2.20	21.58 ± 2.20
	Range	18.59 – 24.76	18.59 – 24.76
Other Factors			

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
20	Subject withdrawn because subject did not report for Period II	Period I Washout	Yes (Subject No. 25)

* Subject No. 7 did not have concentrations above BLQ in period II for drug and metabolite, the subject was excluded from PK analysis.

Subject No. 1 was excluded from PK analysis by the reviewer because of vomiting within the 12-hour dosing interval.

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. 0710050	
	Test	Reference

Gastrointestinal		
Vomiting	00	01*
ENT		
Upper Respiratory Tract Infection	03	01
Total	03	2

*Reviewer's Note: Subject #1 had one episode of vomiting after snacks (within the 12-hour dosing interval) and was dropped from analysis.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

A total of 47 protocol deviations ('cannula blocked' – 8, 'no show' – 23, 'reported late' – 14 and 'difficulty finding in vein' – 2) were reported.

Comments on Dropouts/Adverse Events/Protocol Deviations: No serious adverse events or major protocol deviations occurred to alter the study outcome.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Carbamazepine										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	9.968	19.936	99.680	348.881	1395.523	2990.407	4485.610	5233.212	6977.615	
Inter day Precision (%CV)	1.35	2.45	1.68	1.14	1.36	0.82	2.89	2.85	3.45	
Inter day Accuracy (%Actual)	96.37	104.92	109.32	108.77	105.37	97.29	93.51	92.87	91.59	
Linearity	9.968 – 6977.615									
Linearity Range (ng/mL)	0.9955 – 0.9975									
Sensitivity/LOQ (ng/mL)	9.968									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	30.279	3154.03	5551.093	30.279
Inter day Precision (%CV)	7.63	2.74	4.78	7.63
Inter day Accuracy (%Actual)	99.54	96.47	93.55	99.54

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
RCBL011	09/21/2007	Sample Reassay and reporting of final concentration

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: Acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting Bioequivalence Study, Study No. 0710050 Carbamazepine*									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	214933.6	21.58	145810.6	331748.7	226191.1	20.25	152289.0	311756.2	0.95
AUC∞ (hr *ng/ml)	230053.4	22.19	149390.2	345647.8	244443.3	21.99	154944.2	356783.9	0.94
Cmax (ng/ml)	2210.163	17.13	1504.04	3001.58	2287.791	17.56	1340.22	2847.99	0.97
Tmax* (hr)	25.035	.	12.00	36.00	24.000	.	12.00	32.00	1.04
Kel (hr^{-1})	0.013	23.89	0.01	0.02	0.013	23.13	0.01	0.02	1.01
T1/2 (hr)	57.562	24.11	37.80	89.63	59.286	31.80	37.62	122.69	0.97

*N=23 including subject #1

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated*

Drug name: Carbamazepine Dose: 300 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. 0710050				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (hr *ng/ml)	212467.6	223785.80	94.94	88.48-101.87
AUC∞ (hr *ng/ml)	228397.8	239443.6	95.39	89.17-102.04
Cmax (ng/ml)	2148.03	2330.74	92.16	85.31-99.57

*N=23 including subject #1

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Carbamazepine 300 mg Fasting Bioequivalence Study No. 0710050, N= 22** Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
	carbamazepine				
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	209938.0	222505.0	0.94	87.66	101.56
AUC∞ (ng·hr/mL)	224511.8	239890.9	0.94	87.23	100.41

Cmax (ng/mL)	2172.50	2262.23	0.96	88.63	104.06

**Subject No. 1 was excluded from PK analysis by the reviewer because of vomiting within the 12-hour dosing interval.

Table 17. Additional Study Information, Fasting Study No. 0710050

Carbamazepine		
Root mean square error, AUC0-t	0.1410	
Root mean square error, AUC∞	0.1348	
Root mean square error, Cmax	0.1537	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	22	22
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	3 subjects (< 5% Cmax)	5 subjects (< 5% Cmax)
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	22	0.94	0.84	0.98
Reference	22	0.93	0.78	0.98

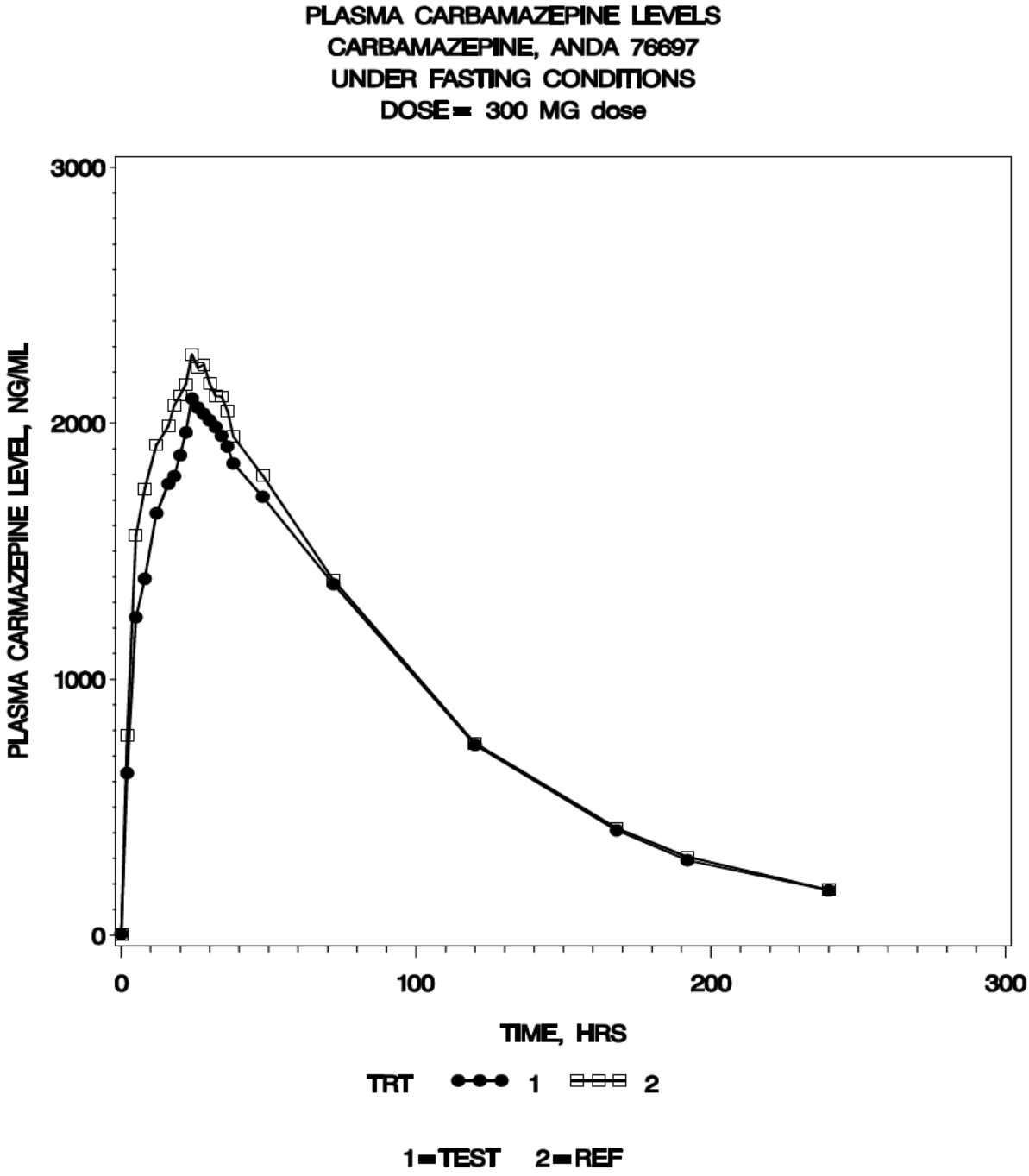
Comments on Pharmacokinetic and Statistical Analysis: The 90% confidence intervals calculated by the reviewer for $LAUC_{0\text{-}t}$, $LAUC_{\infty}$, and LC_{max} are within the 80 to 125% acceptance BE limits after Subject #1 was excluded for vomiting within the dosing interval.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: Acceptable based on the BE results of the parent drug, carbamazepine.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=22)		Reference (n=22)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	5.18	270.68	4.16	196.29	1.24
2.00	625.73	32.39	777.12	32.91	0.81
5.00	1211.61	14.69	1536.35	16.74	0.79
8.00	1358.03	12.17	1733.55	17.27	0.78
12.00	1613.28	12.40	1905.89	14.21	0.85
16.00	1727.56	13.43	1981.29	14.82	0.87
18.00	1759.95	13.11	2061.45	14.32	0.85
20.00	1838.91	17.28	2097.97	15.12	0.88
22.00	1931.50	16.08	2144.92	16.57	0.90
24.00	2064.95	18.70	2255.64	15.25	0.92
26.00	2026.13	18.64	2203.10	16.76	0.92
28.00	2005.36	21.66	2207.73	18.05	0.91
30.00	1981.76	18.70	2138.43	18.01	0.93
32.00	1951.60	19.97	2085.44	18.49	0.94
34.00	1917.27	19.95	2085.23	19.36	0.92
36.00	1878.57	18.54	2029.12	19.82	0.93
38.00	1821.12	20.34	1934.89	20.43	0.94
48.00	1694.33	21.01	1782.95	20.83	0.95
72.00	1358.59	23.44	1369.45	26.83	0.99
120.00	740.11	32.86	746.53	26.88	0.99
168.00	407.35	38.89	415.80	40.33	0.98
192.00	291.92	46.46	303.89	38.94	0.96
240.00	175.25	52.38	177.26	52.20	0.99

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	0712061
Study Title	A randomized, two-treatment, two-period, two-sequence crossover comparative bioavailability study in male subjects under fed conditions.
Clinical Site (Name & Address)	RelClin, Reliance Clinical Pharmacology and Pharmacokinetic Facility, Mumbai – 400701, India
Principal Investigator	Somnath Banerjee, MBBS
Dosing Dates	Period I: 1/15/08; Period II: 2/4/08
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	02/25/08 – 03/07/08
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	53 days

Table 20. Product Information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Carbamazepine 300 mg ER Capsules	Carbatrol® 300 mg capsules
Manufacturer	Nostrum Pharmaceuticals Inc.	Shire Richwood Inc.
Batch/Lot No.	B070068B	6N2897
Manufacture Date	09/2007	
Expiration Date		10/ 2008
Strength	300 mg	300 mg
Dosage Form	Capsule	Capsule
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	102.1%	N/A
Content Uniformity (mean, %CV)	101.5%	
Dose Administered	1 x 300 mg	1 x 300 mg

Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	24*(Subject Nos. 15 and 17 replaced by Subject Nos. 25 and 26, respectively)*
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	AB: 1,4,5,8,10,12,13,15,18,19,22,23,25 BA:2,3,6,7,9,11,14,16,17,20,21,24,26
Blood Sampling Times	0.0, 2.0, 5.0, 8.0, 10.0, 12.0, 13.0, 14.0, 15.0, 16.0, 18.0, 20.0, 24.0, 30.0, 36.0, 48.0, 72.0, 120.0, 168.0, 192.0 and 240.0 hours
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	$-70^0C \pm 15^0C$
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting Before Meal	10 hours
Length of Confinement	At least 12 hours prior to dosing and until 48-hour sample collection
Safety Monitoring	Vital signs were recorded on check-in day, prior to drug administration and 4.0, 9.0 12.0, 24.0, 36.0, 48.0 (check out), 72.0, 120.0, 168.0, 192.0, and 240.0 hours after drug administration.

Standard FDA Meal Used?	Yes

Comments on Study Design: The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. 0712061			
		Treatment Groups	
		Test Product N = 26	Reference Product N = 26
Age (years)	Mean ± SD	25.77 ± 3.36	25.77 ± 3.36
	Range	21 - 33	21 - 33
Age Groups	< 18	0(%)	0(%)
	18 – 40	26(100%)	26(100%)
	41 – 64	0(%)	0(%)
	65 – 75	0(%)	0(%)
	> 75	0(%)	0(%)
Sex	Male	26 (100%)	26 (100%)
	Female	0(0%)	0(0%)
Race	Asian	26 (100%)	26 (100%)
	Black	0(0%)	0(0%)
	Caucasian	0(0%)	0(0%)
	Hispanic	0(0%)	0(0%)
	Other	0(0%)	0(0%)
BMI	Mean + SD	21.37 ± 1.94	21.37 ± 1.94
	Range	18.20 – 24.67	18.20 – 24.67
Other Factors			

Table 23. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
5	Failure to report	II	No
15	Failure to report	II	25
17	Failure to report	II	26
22	Withdrawn for not disclosing full medical history	I	No

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups
	Study No. 0712061

	Test	Reference
Gastrointestinal		
Vomiting	01*	00
SKIN		
Allergic reaction	00	01
Total	1	1

*Subject No. 5 dropped out and did not return to study in Period II.

Table 25. Protocol Deviations, Fed Bioequivalence Study

A total of 37 protocol deviations ('cannula blocked' – 5, 'did not report' – 7, 'reported late' – 16 and 'difficulty finding in vein' – 4, 'slow draw' - 5) were reported.

Comments on Adverse Events/Protocol Deviations: No serious adverse events or major protocol deviations occurred to alter the study outcome.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Carbamazepine										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	10.159	20.318	101.588	355.559	1422.236	3047.649	4571.474	5333.866	7111.182	
Inter day Precision (%CV)	1.04	1.90	2.46	1.76	1.47	3.37	2.19	2.16	1.58	
Inter day Accuracy (%Actual)	96.02	105.78	109.41	106.25	101.38	93.90	95.44	97.82	93.99	
Linearity	0.9968 – 0.9987									
Linearity Range (ng/mL)	10.159 – 7111.182									
Sensitivity/LOQ (ng/mL)	10.159 ng/mL									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	30.213	3147.162	5539.005	
Inter day Precision (%CV)	4.26	6.40	5.51	
Inter day Accuracy (%Actual)	106.73	99.14	96.60	

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
RCBL011	09/21/2007	Sample Reassay and reporting of final concentration

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: Acceptable.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Fed Bioequivalence Study, Study No. 712061 Carbamazepine									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	205282.8	19.13	125672.7	283104.9	232360.6	19.37	163515.5	323524.2	0.88
AUC∞ (hr *ng/ml)	226478.6	22.27	154380.1	357373.5	248442.0	24.38	164796.2	396305.7	0.91
Cmax (ng/ml)	2418.886	16.67	1858.20	3444.78	2670.072	12.57	2243.40	3415.75	0.91
Tmax* (hr)	21.000	.	12.00	36.00	14.000	.	10.00	24.00	1.50
Kel (hr^{-1})	0.014	22.46	0.01	0.02	0.014	24.65	0.01	0.02	1.03
T1/2 (hr)	52.080	23.65	35.07	83.06	54.082	28.92	34.25	99.63	0.96

* Tmax values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Carbamazepine 300 mg Fed Bioequivalence Study No. 0712061, N= 22 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Carbamazepine				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	203184.1	227368.7	0.89	82.59 – 96.69
AUC∞ (hr *ng/ml)	222576.3	240932.7	0.92	87.55 – 97.48
Cmax (ng/ml)	2395.60	2644.59	0.91	86.75 – 94.58

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Carbamazepine 300 mg Fed Bioequivalence Study No. 0712061, N= 22 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Carbamazepine					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	203184.1	227368.7	0.89	82.59	96.69
AUC∞ (hr *ng/ml)	222576.3	240932.7	0.92	87.55	97.48
Cmax (ng/ml)	2395.60	2644.59	0.91	86.75	94.58

Table 32. Additional Study Information

	Carbamazepine	
Root mean square error, AUC0-t	0.1509	
Root mean square error, AUC∞	0.1029	
Root mean square error, Cmax	0.0827	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	22	22
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	7 subjects (< 5% Cmax)	7 subjects (< 5% Cmax)
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	22	0.93	0.35	0.99
Reference	22	0.95	0.80	0.99

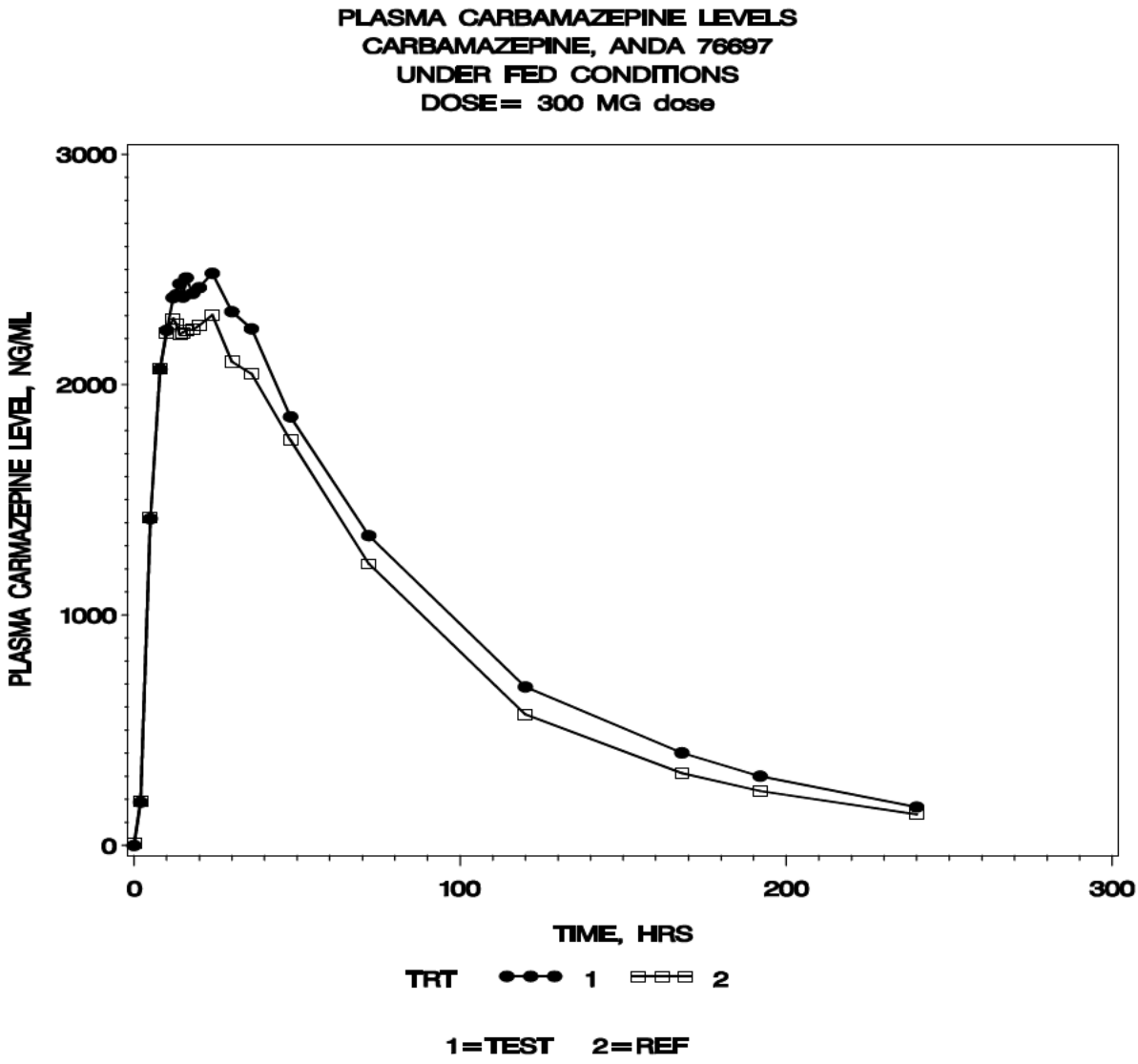
Comments on Pharmacokinetic and Statistical Analysis: The 90% confidence intervals calculated by the reviewer for $LAUC_{0-t}$, $LAUC_{\infty}$, and LC_{max} agree with those of the firm. A median Tmax difference was observed between the test and reference (test-21 hr vs. reference 14 hr) in the fed study. For the test product, there is about 20% decrease in Tmax under fed conditions (vs. fasting conditions). For the reference product, there was about 40% decrease in Tmax under fed conditions (vs. fasting conditions). No appreciable difference in the median Tmax values between the test and reference products was observed in the fasting and sprinkle studies. Since according to the RLD labeling, "Carbatrol® can be taken with or without meals," the difference in median Tmax values between the test and reference may not have any clinical significance.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: Acceptable based on the BE results of the parent drug, carbamazepine.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Carbamazepine					
	Test (n=22)		Reference (n=22)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	10.51	187.26	0.00
2.00	187.99	96.01	192.97	71.62	0.97
5.00	1418.04	23.36	1425.55	30.00	0.99
8.00	2067.38	18.02	2070.20	19.30	1.00
10.00	2236.03	17.26	2222.02	16.34	1.01
12.00	2377.88	15.52	2286.70	16.39	1.04
13.00	2390.19	13.89	2262.14	16.18	1.06
14.00	2437.67	15.80	2218.75	16.12	1.10
15.00	2380.28	15.52	2225.45	16.05	1.07
16.00	2464.09	15.28	2237.09	16.40	1.10
18.00	2396.25	15.22	2238.27	15.37	1.07
20.00	2421.08	13.55	2256.67	16.16	1.07
24.00	2483.15	16.12	2302.18	15.96	1.08
30.00	2317.03	14.76	2099.72	20.96	1.10
36.00	2242.72	18.73	2047.50	17.50	1.10
48.00	1860.23	15.08	1759.55	17.87	1.06
72.00	1344.59	19.15	1222.12	20.43	1.10
120.00	688.07	24.59	568.35	35.18	1.21
168.00	401.95	44.30	313.73	44.11	1.28
192.00	300.54	46.30	236.04	51.90	1.27
240.00	167.02	67.41	135.04	87.31	1.24

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.1.3 Single-dose Fasting (Sprinkle) Bioequivalence Study

4.1.3.1 Study Design

Table 34 Study Information

Study Number	0712062
Study Title	A randomized, two-treatment, two-period, two-sequence crossover comparative bioavailability study in male subjects under fasting (sprinkle) conditions.
Clinical Site (Name & Address)	RelClin, Reliance Clinical Pharmacology and Pharmacokinetic Facility, Mumbai – 400701, India
Principal Investigator	Dhananjay Bakhle, M.D.
Dosing Dates	Period I: 01/24/2008 ; Period II: 2/13/08
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	3/20/08 – 03/29/2008
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	66 days

Table 35. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Carbamazepine 300 mg ER Capsules	Carbatrol® 300 mg capsules
Manufacturer	Nostrum Pharmaceuticals Inc.	Shire Richwood Inc.
Batch/Lot No.	B070068B	6N2897
Manufacture Date	09/2007	
Expiration Date		10/ 2008
Strength	300 mg	300 mg
Dosage Form	Capsule	Capsule
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	102.1%	N/A
Content Uniformity	101.5%	

(mean, %CV)		
Dose Administered	1 x 300 mg	1 x 300 mg
Route of Administration	Oral	Oral

Table 36. Study Design, Single-Dose Fasting (Sprinkle) Bioequivalence Study

Number of Subjects	24* (+ 2 stand-by subjects)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	**AB**: 1,3,6,8,9,11,14,15,18,19,22,23,25 **BA**:2,4,5,7,10,12,13,16,17,20,21,24,26
Blood Sampling Times	(0.0 hour) 2.0, 5.0, 8.0, 12.0, 14.0, 16.0,18.0, 20.0, 22.0, 24.0, 26.0, 28.0, 30.0, 32.0, 34.0, 36.0, 38.0, 48.0, 72.0, 120.0, 168.0, 192.0 and 240.0 hours
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	$-70^0C \pm 15^0C$
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	10 hours
Length of Confinement	At least 12 hours prior to dosing and until 48-hour sample collection
Safety Monitoring	Vital signs were recorded on check-in day, prior to drug administration and 4.0, 9.0 12.0, 24.0, 36.0, 48.0 (check out), 72.0, 120.0, 168.0, 192.0, and 240.0 hours after drug administration.

* Subject No. 14 was dropped and replaced by Subject No. 25.

Comments on Study Design: The study design is acceptable.

4.1.3.2 Clinical Results

Table 37. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting (Sprinkle) Bioequivalence Study No. 0712062			
		Treatment Groups	
		Test Product N = 26	Reference Product N = 26
Age (years)	Mean ± SD	25.42 ± 4.80	25.42 ± 4.80
	Range	19 - 39	19 - 39
Age Groups	< 18	0(%)	0(%)
	18 – 40	26(100%)	26(100%)
	41 – 64	0(%)	0(%)
	65 – 75	0(%)	0(%)
	> 75	0(%)	0(%)
Sex	Male	26 (100%)	26 (100%)
	Female	0(0%)	0(0%)
Race	Asian	100%	100%
	Black	0(%)	0(%)
	Caucasian	0(%)	0(%)
	Hispanic	0(%)	0(%)
	Other	0(%)	0(%)
BMI	Mean + SD	21.26 ± 1.53	21.26 ± 1.53
	Range	18.81 – 24.67	18.81 – 24.67
Other Factors			

Table 38. Dropout Information, Fasting (Sprinkle) Bioequivalence Study

Subject No.	Reason	Period	Replaced?
14	Subject withdrawn due to positive urine test	Period II	Yes (Subject No. 25)

Table 39. Study Adverse Events, Fasting (Sprinkle) Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. 0712062	
	Test	Reference
Gastrointestinal		
Vomiting	01*	00
Skin		
Pityriasis Rosea	01	00
Total	02	0

***Reviewer's Note**: Subject No. 3 had 4-5 episodes of vomiting during the washout period related to consumption of outside food.

Table 40. Protocol Deviations, Fasting (Sprinkle) Bioequivalence Study

A total of 50 protocol deviations ('cannula blocked' – 5, 'did not report' – 14, 'reported late' – 19, 'reported early' – 2, and 'slow draw' - 10) were reported.

Comments on Dropouts/Adverse Events/Protocol Deviations: No serious adverse events or major protocol deviations occurred to alter the study outcome.

4.1.3.3 Bioanalytical Results

Table 41. Assay Validation – Within the Fasting (Sprinkle) Bioequivalence Study

Carbamazepine										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	9.936	19.872	99.361	347.762	1391.048	2980.816	4471.224	5216.428	6955.238	
Inter day Precision (%CV)	1.25	2.21	1.59	1.20	1.64	1.33	1.68	0.79	1.53	
Inter day Accuracy (%Actual)	95.22	109.83	96.81	106.64	104.32	94.94	94.92	98.04	99.29	
Linearity	9.936 – 6955.238									
Linearity Range (ng/mL)	0.9974 – 0.9987									
Sensitivity/LOQ (ng/mL)	9.936									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	29.880	3112.509	5478.017	
Inter day Precision (%CV)	8.83	6.79	4.90	
Inter day Accuracy (%Actual)	95.70	104.39	94.53	

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable

Table 42. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
RCBL011	09/21/2007	Sample Reassay and reporting of final concentration

Table 43. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: Acceptable

4.1.3.4 Pharmacokinetic Results

Table 44. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting (Sprinkle) **Bioequivalence Study, Study No. 0712062**									
Carbamazepine									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	157760.2	24.70	8835 1.92	2448 66.3	172284.7	22.08	1288 60.8	2587 80.5	0.92
AUC∞ (hr *ng/ml)	167121.3	26.81	9028 0.47	2741 41.0	182095.1	25.45	1327 87.6	2938 80.0	0.92
Cmax (ng/ml)	1691.634	16.99	1101.64	2253.60	1919.766	15.97	1396.67	2673.02	0.88
Tmax* (hr)	26.000	.	12.00	38.00	24.000	.	8.00	38.00	1.08
Kel (hr^{-1})	0.014	22.78	0.01	0.02	0.014	19.97	0.01	0.02	1.01
T1/2 (hr)	51.897	23.82	33.20	85.98	52.109	22.22	37.67	84.53	1.00

* Tmax values are presented as median, range

Table 45. Geometric Means and 90% Confidence Intervals - Firm Calculated

Drug name: Carbamazepine **Dose: 300 mg** **Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals**				
Fasting (Sprinkle) Bioequivalence Study, Study Study No. 0712062				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	153180.1	168673.0	0.91	85.36 – 96.62
AUC∞ (hr *ng/ml)	161477.4	177183.9	0.91	85.57 -97.07
Cmax (ng/ml)	1667.70	1896.23	0.88	82.72 – 93.51

Table 46. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Drug name: Carbamazepine **Dose: 300 mg** **Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals**					
Fasting (Sprinkle) Bioequivalence Study, Study No. 0712062					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	153180.1	168673.0	0.91	85.36	96.62
AUC∞ (hr *ng/ml)	161477.4	177183.9	0.91	85.57	97.07
Cmax (ng/ml)	1667.70	1896.23	0.88	82.72	93.51

Table 47. Additional Study Information, Fasting (Sprinkle) Study No. 0712062

Carbamazepine		
Root mean square error, AUC0-t	0.1250	
Root mean square error, AUC∞	0.1272	
Root mean square error, Cmax	0.1236	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	24	24
Do you agree or disagree with firm's decision?	Yes	Yes
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	None	None
first measurable drug concentration as Cmax	3 subjects (< 5% Cmax)	1 subject (< 5% Cmax)
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	24	0.95	0.86	0.99
Reference	24	0.95	0.87	0.99

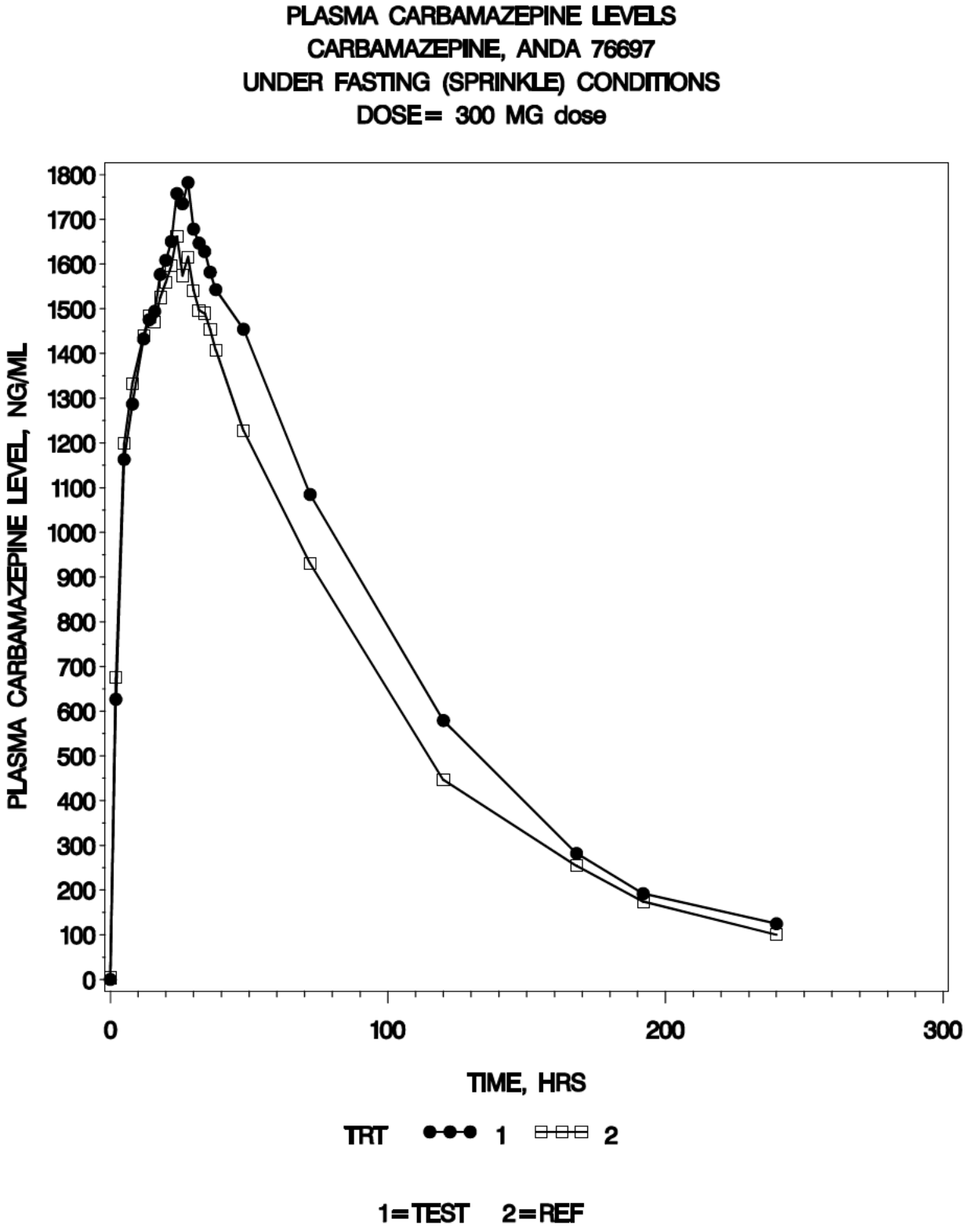
Comments on Pharmacokinetic and Statistical Analysis: The 90% confidence intervals calculated by the reviewer for $LAUC_{0\text{-}t}$, $LAUC_{\infty}$, and LC_{max} agree with those reported by the firm.

Summary and Conclusions, Single-Dose Fasting (Sprinkle) Bioequivalence Study: Acceptable based on the BE results of the parent drug, carbamazepine.

Table 48. Mean Plasma Concentrations, Single-Dose Fasting (Sprinkle) Bioequivalence Study

	Test (n=24)		Reference (n=24)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	4.08	239.27	0.00
2.00	626.52	38.23	675.27	35.16	0.93
5.00	1163.01	20.02	1199.67	28.92	0.97
8.00	1287.07	18.29	1332.80	27.66	0.97
12.00	1432.73	18.13	1440.75	24.68	0.99
14.00	1475.48	18.49	1484.50	21.50	0.99
16.00	1494.43	18.21	1469.75	21.34	1.02
18.00	1576.94	16.32	1525.26	17.84	1.03
20.00	1608.63	14.31	1559.53	17.41	1.03
22.00	1650.80	13.82	1597.18	19.73	1.03
24.00	1757.71	16.75	1661.92	17.75	1.06
26.00	1735.14	18.45	1574.79	16.11	1.10
28.00	1782.43	19.15	1615.96	18.48	1.10
30.00	1678.21	18.49	1541.46	17.84	1.09
32.00	1646.95	19.10	1497.07	17.06	1.10
34.00	1628.13	20.22	1490.00	18.51	1.09
36.00	1582.04	20.12	1453.82	17.18	1.09
38.00	1542.89	20.12	1407.53	19.16	1.10
48.00	1454.35	21.45	1227.35	23.46	1.18
72.00	1084.81	24.72	930.32	24.80	1.17
120.00	579.28	34.75	446.35	33.87	1.30
168.00	281.79	47.04	254.00	52.96	1.11
192.00	191.82	57.69	174.01	64.02	1.10
240.00	124.61	66.70	100.11	66.27	1.24

Figure 3. Mean Plasma Concentrations, Single-Dose Fasting (Sprinkle) Bioequivalence Study



4.2 Formulation Data

Ingredient	% W/W	MG/CAPSULE		
		300 MG	200 MG	100 MG
Carbamazepine	(b) (4)	300.00	200.00	100.00
(b) (4)		(b) (4)		
Sodium Lauryl Sulfate				
(b) (4)				
Total	**100.00**			

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	The RLD consist of 3 different types – immediate release (IMA), sustained release (IMB) and enteric release (IMC) pellets combined in a special ratio ((b) (4) and (b) (4)%, respectively) for BID dosing. The generic product contains only a single type of beads for BID dosing. The test formulation for all three strengths are (b) (4) (b) (4) and are proportionally similar. ***The Chemistry Division is advised to determine the formulation suitability for BE studies.***

RLD Formulation: Carbatrol® Capsules- 100 mg, 200 mg, 300 mg

Ingredient	Grade	100 mg mg/capsule	200 mg mg/capsule	300 mg mg/capsule	% pe
Carbamazepine	USP	100.0	200.0	300.0	
					(b) (4)

4.3 Dissolution Data

Dissolution Review Path	None

http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date
Carbamazepine	Capsule (Extended Release)	II (Paddle)	75	First 4 hours: Dilute Acid, pH 1.1 with 1.8% B-cyclodextrin. After 4 hours: 50 mM Phosphate Buffer, pH 7.5 with 1.1% B-cyclodextrin.	First 4 h: 600 mL. After 4 h: 1000 mL	1, 2, 4, 8, and 10 hours	07/25/2007

Table 49. Dissolution Data

Dissolution Conditions	**Apparatus:**	Paddle
	Speed of Rotation:	100 rpm
	Medium:	0.1% SLS, pH 1.2 buffer
	Volume:	900 mL
	Temperature:	Not provided
Firm's Proposed Specifications	Not provided	
Dissolution Testing Site (Name, Address)	Not provided	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (in hours)**						
						1	**2**	**4**	**6**	**8**	**10**	
Study Report #:		Test Product	300 mg Capsule	12	Mean	35	48	65	74	80	84	85
					Range	(b) (4)						
					%CV	3.7	1.8	1.8	1.6	2.2	4.1	0.9
Study Report #:		Reference Product	300 mg Capsule	12	Mean							
					Range							
					%CV							
Study Report #:		Test Product	200 mg Capsule	12	Mean	32	46	63	74	81	86	90
					Range	(b) (4)						
					%CV	2.4	3.6	3.2	2.3	2.5	2.1	2.3
Study Report #:		Reference Product	200 mg Capsule	12	Mean							
					Range							
					%CV							
Study Report #:		Test Product	100 mg Capsule	12	Mean	31	46	64	76	84	89	94
					Range	(b) (4)						
					%CV	3.7	4.4	2.2	1.6	1.5	1.2	1.2
Study		Reference Product	100	12	Mean							

y Repo rt #:			mg Capsu le		Rang e							
					%CV							

Reviewer's Note: The firm did not provide dissolution data for the RLD. No information on the test batch/lot number used in dissolution was provided. The firm's dissolution testing method is different from the FDA method for this drug product posted on the FDA external dissolution database.

Figure 4. Dissolution Profiles

N/A

4.4 Detailed Regulatory History (If Applicable)

N/A

4.5 Consult Reviews

N/A

DEFICIENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76697

APPLICANT: Nostrum Pharmaceuticals Inc

DRUG PRODUCT: Carbamazepine Extended Release Capsules, 100 mg, 200 mg and 300 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. The dissolution testing is incomplete. Please repeat dissolution testing using the following FDA-recommended dissolution method for all three strengths:

Apparatus:	USP Apparatus 2 (paddle)	
Rotation speed	75 rpm	
Medium	**Temperature**: 37°C	**Volume**
First 4 hours;	Dilute acid, pH 1.1 with 1.8 % B-cyclodextrin.	600 mL
After 4 hours	50 mM Phosphate Buffer, pH 7.5 with 1.1 % B cyclodextrin.	1000 mL.
Sampling times	**1, 2, 4, 8 and 10 hours.**	

The method is posted on the FDA dissolution website

2. Please conduct dissolution testing in three additional media (0.1N HCl, acetate buffer pH 4.5 and phosphate buffer 6.8) for the highest strength, 300 mg, per CDER 2003 BA/BE Guidance for modified release drug products.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 76697

Completed Assignment for 76697 ID: 5652

Reviewer: Nwakama, Patrick **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5652	4/28/2008	Bioequivalence Study	Fasting Study	1	1
5652	4/28/2008	Bioequivalence Study	Fed Study	1	1
5652	4/28/2008	Bioequivalence Study	Fasting Study	1	1
5652	4/28/2008	Other	Dissolution Waiver	1	1
5652	4/28/2008	Other	Dissolution Waiver	1	1
				Bean Total:	5

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Typical BE Study Applications

BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Metabolite	1
Fasting Study Total	*4*
BE Study Fed	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Metabolite	1
Fed Study Total	*4*
BE Study Fasting (Sprinkle)	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Metabolite	1
Fed Study Total	*4*

Dissolution Study/ Dissolution Waiver(s)	
Dissolution Study (not done under dissolution review)	1
Strength 1 (DIW)	0.5
Strength 2 (DIW)	0.5
Dissolution Study/Waiver Total	*2.0*

Grand Total	**14.0**

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

/s/

Patrick E. Nwakama
7/15/2008 10:22:46 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
7/17/2008 08:41:51 PM
BIOPHARMACEUTICS

Moheb H. Makary
7/18/2008 07:13:54 AM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Nioequivalence II

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76697		
Drug Product Name	Carbamazepine Extended Release Capsules		
Strength(s)	100 mg, 200 mg and 300 mg		
Applicant Name	Nostrum Pharmaceuticals, LLC		
Address	1800 North Topping Avenue Kansas City, MO 64120		
Applicant's Point of Contact	Dhiren N. Shah, Ph.D., RAC		
Contact's Telephone Number	816-308-4970		
Contact's Fax Number	816-308-4975		
Original Submission Date(s)	March 26, 2003		
Submission Date(s) of Amendment(s) Under Review	September 3, 2008 (amendment) September 25, 2008 (telephone amendment)		
Reviewer	Kimberly W. Raines, Ph.D.		
Study Number (s)	0710050	0712061	0712062
Study Type (s)	Fasting	Fed	Re-dose Fed
Strength (s)	1 × 300 mg	1 × 300 mg	1 × 300 mg
Clinical Site	RelClin, Reliance Clinical Pharmacology and Pharmacokinetic Facility		
Clinical Site Address	Rabale, Navi Mumbai, India		
Analytical Site	(b) (4)		
Analytical Site Address			
OUTCOME DECISION	**INCOMPLETE**		

REVIEW OF AN AMENDMENT

1 EXECUTIVE SUMMARY

Nostrum Pharmaceuticals LLC submitted the current amendment in response to the DBE's Bioequivalence Review deficiency letter dated July 31, 2008 and telephone amendment initiated September 18, 2008, for its Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg. The Division of Bioequivalence (DBE) asked the firm to respond to the following deficiencies:

Please repeat dissolution testing using the following FDA-recommended dissolution method for all three strengths of the test and reference products:

Apparatus:	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm
Medium	
First 4 hours:	Dilute acid, pH 1.1 with 1.8% β-cyclodextrin, 600 mL
After 4 hours:	50 mM Phosphate Buffer, pH 7.5 with 1.1% β-cyclodextrin, 1000 mL
Sampling Times	1, 2, 4, 8 and 10 hours

In addition, the firm was asked to conduct dissolution testing in three additional media (0.1N HCl, acetate buffer pH 4.5 and phosphate buffer 6.8) for the highest strength, 300 mg, of the test and reference products per CDER 2003 BA/BE Guidance for modified release drug products, as well as, perform dissolution testing between the highest strength of Carbatrol® and Nostrum's Carbamazepine ER Capsules, 300 mg using their proposed dissolution method (0.1% SLS pH 1.2).

In this amendment, the firm submitted comparative dissolution testing using the FDA-recommended method on all strengths, and comparative dissolution testing using its proposed method on the 300 mg strength. The firm also submitted dissolution testing in three additional media for the highest strength of the test and reference products.

Based on the submitted data, the DBE recommends that the firm use the FDA-recommended dissolution method for its Carbamazepine ER Capsules, 100 mg, 200 mg and 300 mg. The DBE recommends the following data driven dissolution testing specifications for Nostrum's Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg:

300 mg strength	1hr:	(b) (4)
	4 hr:	
	8 hr:	
100 mg and 200 mg strengths	1 hr:	
	4 hr:	
	8 hr:	

The firm should indicate if it accepts the DBE recommended dissolution method and specifications for its Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is incomplete.

2 TABLE OF CONTENTS

3 BACKGROUND

In the original application (March 26, 2003), Nostrum Pharmaceuticals previously submitted fasting and fed bioequivalence (BE) studies on its Carbamazepine ER Capsules, 300 mg. Statistical analyses of the plasma concentration data for carbamazepine and carbamazepine 10, 11-epoxide in both studies demonstrated bioequivalence. The two BE studies were acceptable but the application was incomplete because the additional fasting (Sprinkle) BE study was not conducted and the dissolution testing was not performed according to the FDA-recommended method. In the original amendment (October 5, 2004), the firm submitted the results of the sprinkle fasting study. Although the statistical analysis of Carbamazepine pharmacokinetic data demonstrated bioequivalence, the analysis of the active metabolite, carbamazepine 10, 11-epoxide, by the firm did not pass BE criteria. The FDA found the BE studies acceptable based on the results of parent drug alone. However, the application was found incomplete pending the firm's acknowledgement of the FDA's recommended dissolution method and specifications [900 mL, pH 1.2 buffer (with 0.1% SLS), Apparatus I (Basket); 100 rpm and specifications - 1 hr: (b) (4)%, 4 hr: (b) (4)%, 8 hr: (b) (4)%, 12 hr: NLT (b) (4)%].

Following a series of communications between the OGD and the firm, OGD Chemistry sent a Major deficiency letter informing the firm that their original biobatch has been rendered unsuitable for in vivo bioequivalence studies due to (b) (4)

The firm then submitted results of three new BE (fasting, fed and fasting sprinkle) studies comparing newly formulated Nostrum Pharmaceuticals Carbamazepine Extended Release Capsules, 300 mg to the corresponding reference product, Shire's Carbatrol® Extended Release Capsules, 300mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. In all three BE studies, the parent drug, carbamazepine, met the 90% CI acceptance criteria for AUCT, AUCI and Cmax.

The firm conducted comparative dissolution testing on all strengths using its own method. The dissolution results were not acceptable. The firm was asked to repeat dissolution testing using the FDA-recommended dissolution method for this drug product as posted on the external website for all three strengths and in three additional pH media for the highest strength, 300 mg, per CDER 2003 BA/BE Guidance for modified release drug products.

The firm responded to these deficiencies in amendments dated September 3, 2008 and September 25, 2008.

4 REVIEW OF AMENDMENT

Deficiency #1:

The dissolution testing is incomplete. Please repeat dissolution testing using the following FDA-recommended dissolution method for all strengths (test and reference):

Apparatus:	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm
Medium	
First 4 hours:	Dilute acid, pH 1.1 with 1.8% β –cyclodextrin, 600 mL
After 4 hours:	50 mM Phosphate Buffer, pH 7.5 with 1.1% β – cyclodextrin, 1000 mL
Sampling Times	1, 2, 4, 8 and 10 hours

The method is posted on the FDA dissolution website.

Firm's Response #1:

A summary of dissolution release profiles using method posted on FDA dissolution website are given below in **Table 3.2.P.5.4.1** and **Figure 3.2.P.5.4.1**. Raw data for dissolution of all 12 units is given within **Table 3.2.P.5.4.1.A.1** for 300 mg, **Table 3.2.P.5.4.1.A.2** for 200 mg, and **Table 3.2.P.5.4.1.A.3** for 100 mg strengths of the test products.

A summary of dissolution release profiles for Carbatrol® using method posted on FDA dissolution website are given below in **Table 3.2.P.5.4.1** and **Figure 3.2.P.5.4.1**. Raw data for dissolution on all 12 units is given within **Table 3.2.P.5.4.1.A.1** for 300 mg, **Table 3.2.P.5.4.1.A.2** for 200 mg, and **Table 3.2.P.5.4.1.A.3** for 100 mg strengths. (*The reviewer has provided the raw data as attachment #1 at the end of the review.*)

Table 3.2.P.5.4.1: Dissolution release for all three strengths of Carbatrol® with FDA website method

Apparatus	USP Apparatus 2 (paddle)	
Speed	75 rpm	
Medium	**Temperature**: 37º C	**Volume**
	First 4 hours: Dilute acid, pH 1.1 with 1.8% β-Cyclodextrin	600mL
	After 4 hours: 50mM Phosphate buffer, pH 7.5 with 1.1% β -Cyclodextrin	1000mL
Number of Units tested	12	

Sampling Time	**300mg**	**200mg**	**100mg**
	Average % Carbamazepine released		
1	36	37	39
2	53	55	56
4	65	67	67
8	99	103	101
10	100	103	101

Table 3.2.P.5.4.1: Dissolution release for all three strengths of the test product with FDA website method

Apparatus	USP Apparatus 2 (paddle)	
Speed	75 rpm	
Medium	**Temperature**: 37° C	**Volume**
	First 4 hours: Dilute acid, pH 1.1 with 1.8% β-Cyclodextrin	600mL
	After 4 hours: 50mM Phosphate buffer, pH 7.5 with 1.1% β -Cyclodextrin	1000mL
Number of Units tested	12	

Sampling Time	**300mg**	**200mg**	**100mg**
	Average % Carbamazepine released		
0	0	0	0
1	30	33	33
2	47	51	53
4	69	75	79
8	82	92	97
10	87	95	102

Figure 3.2.P.5.4.1: Plotted dissolution release profile for all three strengths of Carbatrol® with FDA website Method

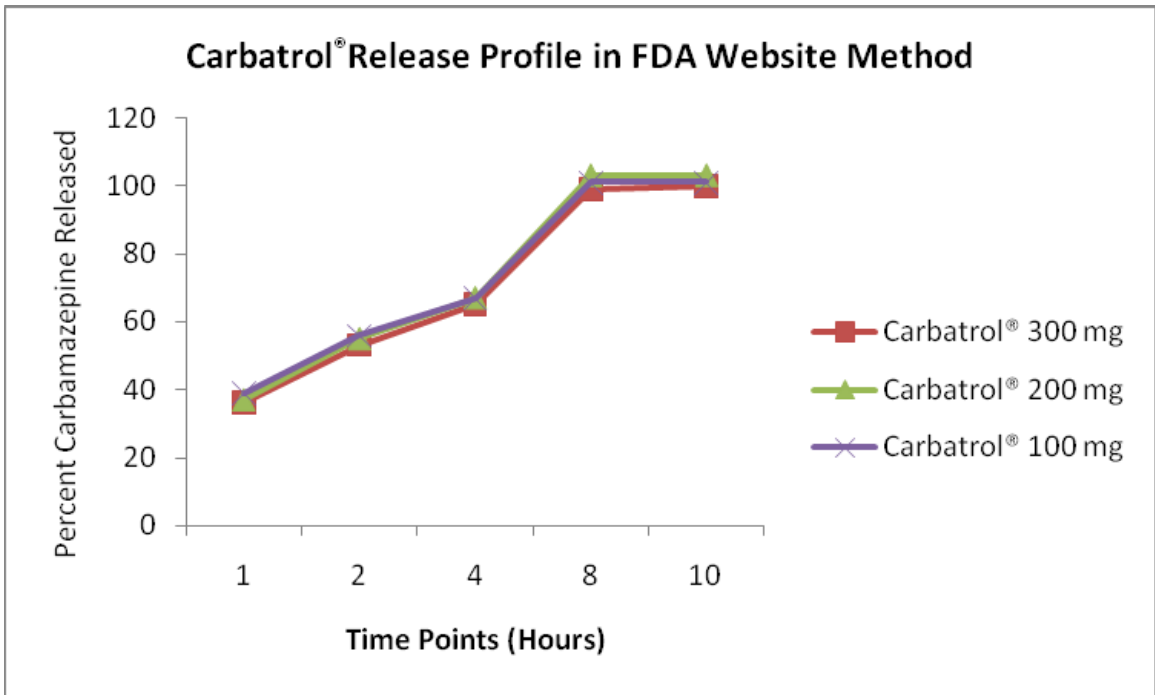
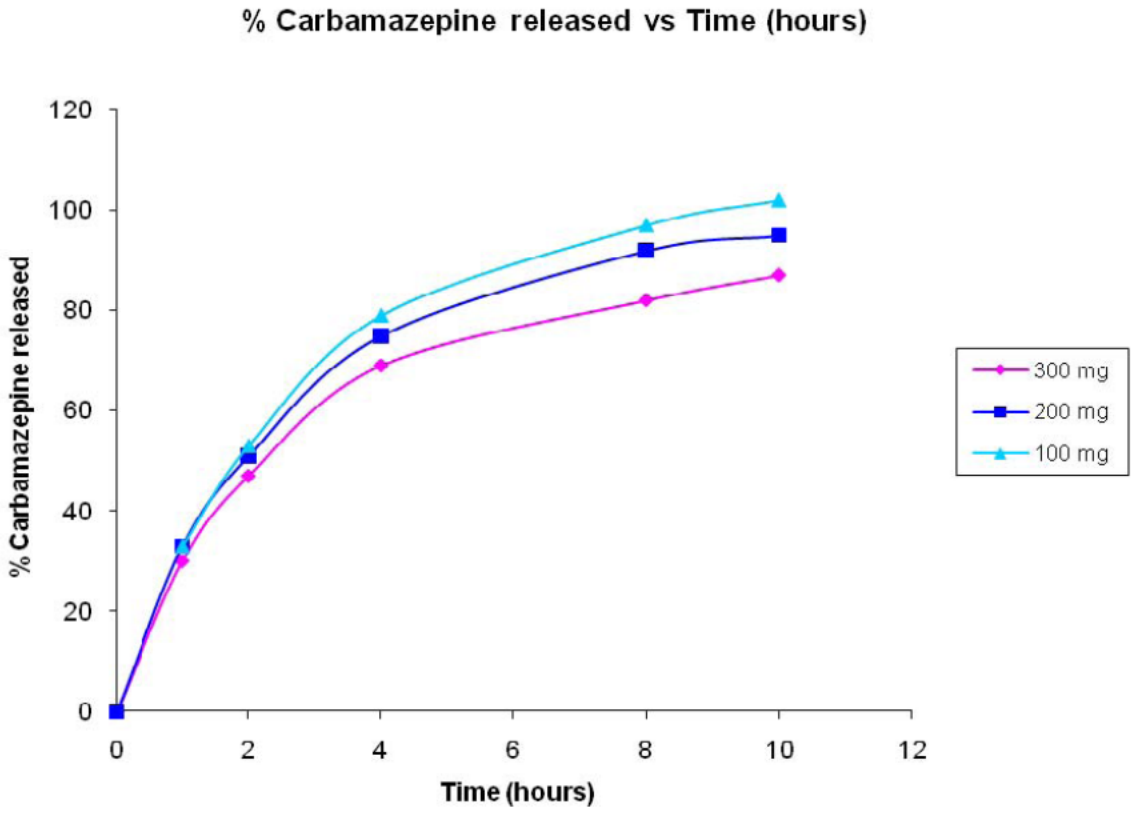


Figure 3.2.P.5.4.1: Plotted dissolution release profile for all three strengths with FDA website method



Nostrum Laboratories Inc. (NLI) would like to make note the following observations for the agency's consideration for its Carbamazepine ER Capsules dissolution release testing:

1. Unlike the Reference Listed Drug (RLD) – Carbatrol® (which is composed of three different types of beads- immediate release, extended release, and enteric release) NLI's Carbamazepine ER Capsules consist of same type of single [redacted] (b) (4) beads for all three strengths.

2. NLI's Carbamazepine ER Capsules are manufactured using the excipients [redacted] (b) (4). Since these excipients are not affected by pH change, NLI believes pH change would also have no impact on rate of Carbamazepine release from NLI's Drug product.

3. The comparison of dissolution release profiles between various media (**Table 3.2.P.5.4.2**, **Table 3.2.P.5.4.3** and **Table 3.2.P.5.4.4** and their sub-tables) on the highest strength show similar dissolution release profiles regardless of varying pH from NLI's Carbamazepine ER Capsules.

4. The dissolution testing method on FDA's website is tedious, complicated, and not specifically designed for NLI's Carbamazepine ER Capsules.

Reviewer's Comment #1:

The FDA-recommended dissolution testing method displays adequate dissolution while maintaining good discrimination (please see Additional Comments – Dissolution Consultation). In addition, the FDA-recommended dissolution method demonstrates similarity between strengths, supporting the waiver of *in vivo* testing of the lower strengths; 200 mg and 100 mg (please see F2 metric calculations provided below).

Based on the submitted data, the DBE recommends the following dissolution specifications for Nostrum's Carbamazepine Extended Release Capsules:

300 mg strength	1hr: (b) (4) 4 hr: % 8 hr: NLT (b) (4)%
100 mg and 200 mg strengths	1 hr: (b) (4)% 4 hr: % 8 hr: NLT (b) (4)%

The firm should indicate if it accepts the FDA-recommended dissolution method and specifications for its Carbamazepine Extended Release Capsules, 100 mg, 200 mg and 300 mg.

The reviewer acknowledges the firm's comments regarding formulation differences between the test and the reference listed drug products, but based on the dissolution data submitted by the firm, the DBE reiterates that the firm uses the FDA-recommended dissolution method as listed on the FDA's dissolution website.

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
300 mg	200 mg	56.85	78.49
300 mg	100 mg	50.73	78.12

Deficiency #2:

Please conduct dissolution testing in three additional media (0.1N HCl, acetate buffer, pH 4.5 and phosphate buffer, pH 6.8) for both the RLD and test product highest strength, 300 mg, per CDER 2003 BA/BE guidance for modified release drug products.

Firm's Response #2:

NLI conducted dissolution testing on the highest strength of the RLD, Carbatrol® 300 mg and test product, Nostrum's Carbamazepine ER Capsules, 300 mg, in the three media as requested by the Agency. Summary of dissolution testing results for the same are provided here within **Table 3.2.P.5.4.2** (raw data is reported within sub-tables A, B, and

C), and plots for the dissolution release profiles are provided below within **Figure 3.2.P.5.4.2**. Raw data for dissolution release testing if provided with **Table 3.2.P.5.4.2.A** for 0.1N HCl, **Table 3.2.P.5.4.2.B** for acetate buffer pH 4.5, and **Table 3.2.P.5.4.2.C** phosphate buffer, pH 6.8. (*The reviewer has provided the raw data as attachment #2 at the end of the review.*)

Table 3.2.P.5.4.2: Summary of Dissolution release for Carbatrol® 300mg (6N2897) in three different media

Apparatus	USP Apparatus 2 (paddle)		
Speed	75 rpm		
Temperature	37° C		
Medium	0.1 N HCl	Acetate buffer pH 4.5	Phosphate buffer pH 6.8
Volume	900 mL	900 mL	900 mL
Number of Units tested	12	12	12
Sampling Time	**Average % Carbamazepine released**		
1	21	20	27
2	32	29	39
4	43	40	52
8	53	50	61
10	56	52	61

Table 3.2.P.5.4.4: Dissolution release for 300mg (B070068) strength in three different media

Apparatus	USP Apparatus 2 (paddle)		
Speed	75 rpm		
Temperature	37° C		
Medium	0.1 N HCl	Acetate buffer pH 4.5	Phosphate buffer pH 6.8
Volume	1000 mL	1000 mL	1000 mL
Number of Units tested	12	12	12
Sampling Time	**Average % Carbamazepine released**		
0	0	0	0
1	18	17	18
2	29	29	28
4	44	45	42
8	59	62	58
10	66	66	62

Figure 3.2.P.5.4.2: Plotted dissolution release profile for Carbatrol® 300 mg (Lot No 6N2897) in three different media

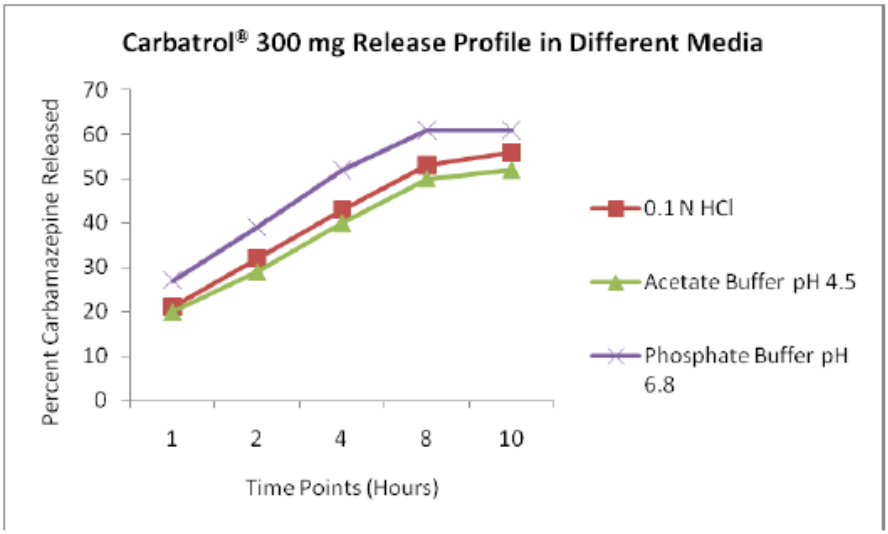
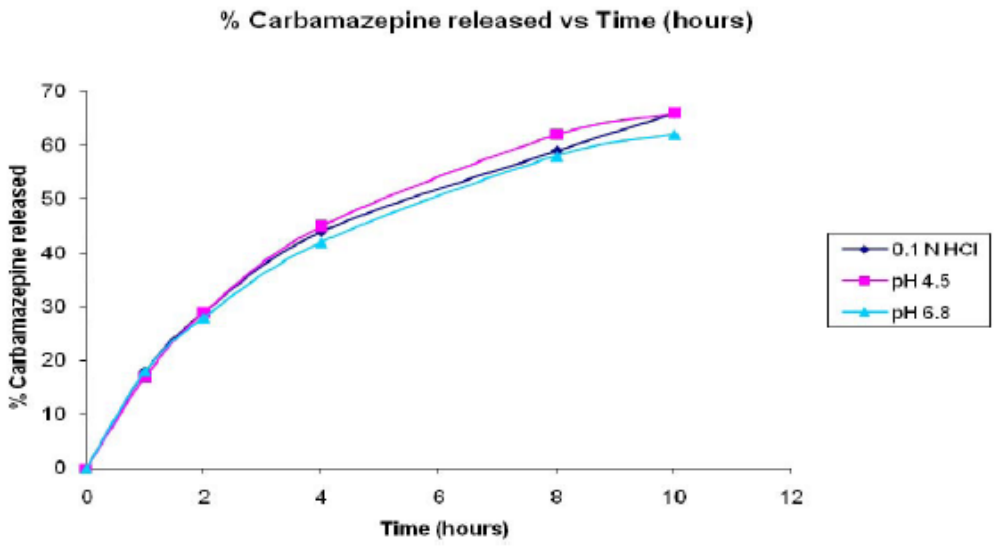


Figure 3.2.P.5.4.4: Plotted dissolution release profile for 300 mg strength in three different media



Reviewer's Comment #2:

The firm's submitted data indicates that the test and reference listed drug products display similar dissolution profiles in the three additional media (0.1N HCl, pH 4.5 and pH 6.8).

The firm's response is **acceptable**.

Deficiency #3:

Please conduct comparative dissolution testing between the highest strength of Carbatrol® and Nostrum's Carbamazepine ER Capsules using the firm's proposed method (0.1% SLS pH 1.2).

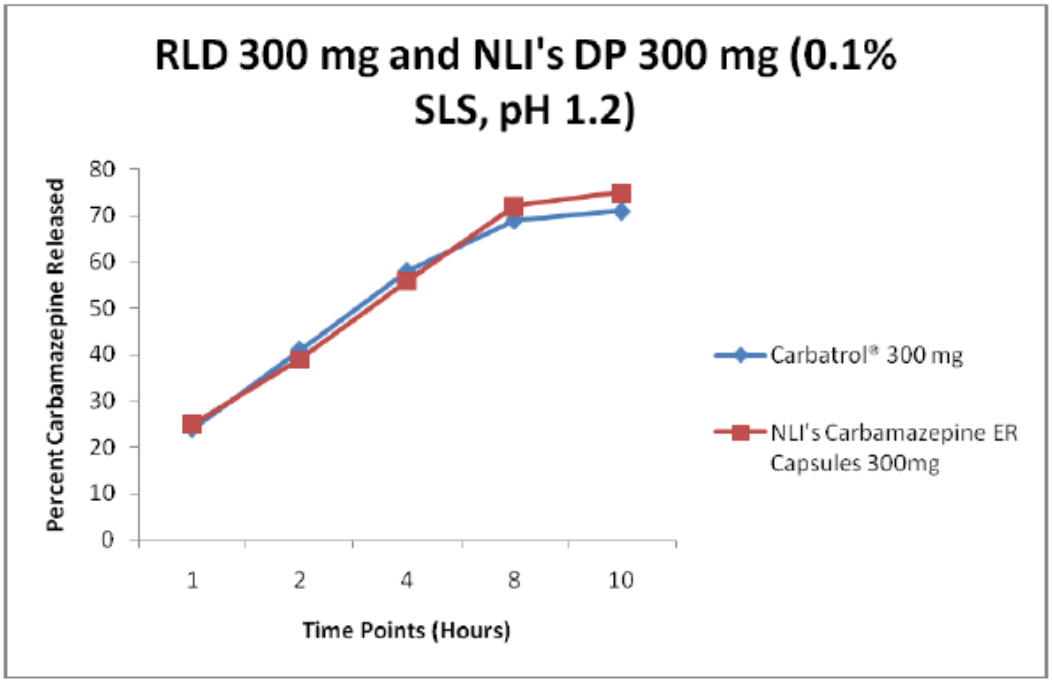
Firm's Response #3:

In addition, NLI also conducted comparison dissolution testing between the highest strength of Carbatrol® and NLI's Carbamazepine ER Capsules 300 mg using 0.1% SLS pH 1.2. The summary results of this testing are given below within **Table 3.2.P.5.4.3** with comparison plot within **Figure 3.2.P.5.4.3**. Raw data for dissolution release of Carbatrol® 300 mg is available within **Table 3.2.P.5.4.3.A** while raw data for dissolution release of NLI's Carbamazepine ER Capsules 300 mg is available within **Table 3.2.P.5.4.3.B.**

Table 3.2.P.5.4.3: Summary of dissolution release comparison of Carbatrol® 300 and NLI's Carbamazepine ER Capsules 300mg

Apparatus	USP Apparatus 1 (basket)	
Speed	100 rpm	
Method	**FDA Nov 19th, 2004 Deficiency Letter Method**	
Medium	0.1 % SLS, pH 1.2	
Number of Units tested	12	
Volume	900 mL	
Sampling Time	**Carbatrol® 300 mg**	**NLI's Carbamazepine ER Capsules 300mg**
	Average % Carbamazepine released	
1	24	25
2	41	39
4	58	56
8	69	72
10	71	75

Figure 3.2.P.5.4.3: Plot of Summary of dissolution release comparison of Carbatrol® 300 and NLI's Carbamazepine ER Capsules 300mg using 0/1% SLS pH 1.2



Reviewer's Comment #3:

The dissolution testing data submitted by the firm using their proposed method (0.1% SLS, pH 1.2) did not demonstrate adequate and discriminating dissolution for the test or reference listed drug products. As seen in the firm's plot (Figure 3.2.P.5.4.3) dissolution has not reached a definite plateau at the 10 hour sampling time point and complete dissolution has not been achieved (i.e. less than 80% dissolved at 10 hr). Therefore, the reviewer recommends that the firm utilize the FDA-recommended dissolution method for future testing.

The firm's response is **acceptable**.

Reviewer's Overall Comments:

Internal Dissolution Database (Not for release under FOI)

Carbamazepine (ER)

Dosage Form: Capsule (ER)

Medium: First 4hr:Dilute Acid, pH1.1 with 1.8% cyclodextrin. After 4 hr: 50mM Phosphate buffer, pH7.5 w/ 1.1%cyclodextrin

Apparatus: II (Paddle)

Speed/RPMs: 75

Modify Date: 6/27/2007

Sampling Times:

Volume: First 4 hr: 600 mL, After 4 hr:1000 mL

Notes:

Specification: 1hr (b) (4), 4hr: (b) (4), 8hr:NLT (b) (4)%

In addition, during the telephone amendment the firm was asked to provide detailed descriptions of all dissolution methods employed for the drug product and a justification for using the 0.1% SLS pH 1.2 dissolution media (please see Additional Attachments Email from Firm Representative). The firm did not address these issues in the submitted amendments.

The reviewer feels comfortable with the firm's dissolution methodology as the firm obtained dissolution data on the reference listed drug product similar to in-house dissolution data the DBE has on Carbatrol®. In addition, since the DBE is not recommending the firm's proposed dissolution method (0.1% SLS pH 1.2) it is not necessary for the firm to submit justification for this method.

The firm's response is **acceptable**; the reviewer no longer needs this information.

Attachment #1:

Tables 3.2.P.5.4.1.A: Raw Data for Dissolution release for all three strengths of Carbatrol® with FDA website method

Table 3.2.P.5.4.1.A.1 Carbatrol® 300 mg (6N2897)

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	*First 4 hours:* Dilute acid, pH 1.1 with 1.8% β -Cyclodextrin *After 4 hours:* 50mM Phosphate buffer, pH 7.5 with 1.1% β -Cyclodextrin	600 mL 1000 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics		Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)			8 hour	1	(b) (4)		
	2					2			
	3					3			
	4		Average	36		4		Average	99
	5		Std Dev	2.0		5		Std Dev	2.0
	6		RSD %	5.6		6		RSD %	2.0
	7		Maximum	(b) (4)		7		Maximum	(b) (4)
	8		Minimum			8		Minimum	
	9					9			
	10					10			
	11					11			
	12					12			
2 hour	1				10 hour	1			
	2					2			
	3					3			
	4		Average	53		4		Average	100
	5		Std Dev	1.7		5		Std Dev	1.9
	6		RSD %	3.2		6		RSD %	1.9
	7		Maximum	(b) (4)		7		Maximum	(b) (4)
	8		Minimum			8		Minimum	
	9					9			
	10					10			
	11					11			
	12					12			
4 hour	1								
	2								
	3								
	4		Average	65					
	5		Std Dev	1.1					
	6		RSD %	1.8					
	7		Maximum	(b) (4)					
	8		Minimum						
	9								
	10								
	11								
	12								

Table 3.2.P.5.4.1.A.2 Carbatrol® 200 mg (6P3017)

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	*First 4 hours:* Dilute acid, pH 1.1 with 1.8% β-Cyclodextrin *After 4 hours*: 50mM Phosphate buffer, pH 7.5 with 1.1% β-Cyclodextrin	600 mL 1000 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)		
	2			
	3			
	4		Average	37
	5		Std Dev	2.8
	6		RSD %	7.4
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
2 hour	1			
	2			
	3			
	4		Average	55
	5		Std Dev	2.9
	6		RSD %	5.2
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
4 hour	1			
	2			
	3			
	4		Average	67
	5		Std Dev	1.9
	6		RSD %	2.8
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			

Sampling Time	Vessel	% Carbamazepine Released	Statistics	
8 hour	1	(b) (4)		
	2			
	3			
	4		Average	103
	5		Std Dev	2.4
	6		RSD %	2.3
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
10 hour	1			
	2			
	3			
	4		Average	103
	5		Std Dev	1.8
	6		RSD %	1.7
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			

Table 3.2.P.5.4.1.A.3 Carbatrol® 100 mg (A25571A)

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	*First 4 hours*: Dilute acid, pH 1.1 with 1.8% β-Cyclodextrin *After 4 hours*: 50mM Phosphate buffer, pH 7.5 with 1.1% β-Cyclodextrin	600 mL 1000 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)		
	2			
	3			
	4		Average	39
	5		Std Dev	4.4
	6		RSD %	11.3
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
2 hour	1			
	2			
	3			
	4		Average	56
	5		Std Dev	4.5
	6		RSD %	8.0
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
4 hour	1			
	2			
	3			
	4		Average	67
	5		Std Dev	3.4
	6		RSD %	5.0
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
8 hour	1	(b) (4)		
	2			
	3			
	4		Average	101
	5		Std Dev	2.1
	6		RSD %	2.1
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
10 hour	1			
	2			
	3			
	4		Average	101
	5		Std Dev	1.6
	6		RSD %	1.6
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			

Tables 3.2.P.5.4.1.A: Raw Data for Dissolution release for all three strengths with FDA website method

Table 3.2.P.5.4.1.A.1 Carbamazepine ER capsules 300 mg (B070068)

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	*First 4 hours:* Dilute acid, pH 1.1 with 1.8% β -Cyclodextrin *After 4 hours*: 50mM Phosphate buffer, pH 7.5 with 1.1% β -Cyclodextrin	600 mL 1000 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics		Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)			8 hour	1	(b) (4)		
	2					2			
	3					3			
	4		Average	30		4		Average	82
	5		Std Dev	0.8		5		Std Dev	3.2
	6		RSD %	2.6		6		RSD %	3.8
	7		Maximum	(b) (4)		7		Maximum	(b) (4)
	8		Minimum			8		Minimum	
	9					9			
	10					10			
	11					11			
	12					12			
2 hour	1				10 hour	1			
	2					2			
	3					3			
	4		Average	47		4		Average	87
	5		Std Dev	1.5		5		Std Dev	2.9
	6		RSD %	3.2		6		RSD %	3.4
	7		Maximum	(b) (4)		7		Maximum	(b) (4)
	8		Minimum			8		Minimum	
	9					9			
	10					10			
	11					11			
	12					12			
4 hour	1								
	2								
	3								
	4		Average	69					
	5		Std Dev	1.6					
	6		RSD %	2.4					
	7		Maximum	(b) (4)					
	8		Minimum						
	9								
	10								
	11								
	12								

Table 3.2.P.5.4.1.A.2 Carbamazepine ER capsules 200 mg (B070046B)

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	*First 4 hours:* Dilute acid, pH 1.1 with 1.8% β-Cyclodextrin *After 4 hours*: 50mM Phosphate buffer, pH 7.5 with 1.1% β-Cyclodextrin	600 mL 1000 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics		Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)			8 hour	1	(b) (4)		
	2					2			
	3					3			
	4		Average	33		4		Average	92
	5		Std Dev	0.9		5		Std Dev	1.6
	6		RSD %	2.6		6		RSD %	1.8
	7		Maximum	(b) (4)		7		Maximum	(b) (4)
	8		Minimum			8		Minimum	
	9					9			
	10					10			
	11					11			
	12					12			
2 hour	1				10 hour	1			
	2					2			
	3					3			
	4		Average	51		4		Average	95
	5		Std Dev	1.2		5		Std Dev	1.5
	6		RSD %	2.4		6		RSD %	1.5
	7		Maximum	(b) (4)		7		Maximum	(b) (4)
	8		Minimum			8		Minimum	
	9					9			
	10					10			
	11					11			
	12					12			
4 hour	1								
	2								
	3								
	4		Average	75					
	5		Std Dev	2.0					
	6		RSD %	2.7					
	7		Maximum	(b) (4)					
	8		Minimum						
	9								
	10								
	11								
	12								

Table 3.2.P.5.4.1.A.3 Carbamazepine ER capsules 100 mg (B070046A)

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	*First 4 hours:* Dilute acid, pH 1.1 with 1.8% β-Cyclodextrin *After 4 hours*: 50mM Phosphate buffer, pH 7.5 with 1.1% β-Cyclodextrin	600 mL 1000 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)		
	2			
	3			
	4		Average	33
	5		Std Dev	1.2
	6		RSD %	3.6
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
2 hour	1			
	2			
	3			
	4		Average	53
	5		Std Dev	1.1
	6		RSD %	2.1
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
4 hour	1			
	2			
	3			
	4		Average	79
	5		Std Dev	1.3
	6		RSD %	1.7
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
8 hour	1	(b) (4)		
	2			
	3			
	4		Average	97
	5		Std Dev	1.6
	6		RSD %	1.6
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
10 hour	1			
	2			
	3			
	4		Average	102
	5		Std Dev	1.8
	6		RSD %	1.8
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			

Attachment #2

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	0.1 N HCl	900 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics		Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)			8 hour	1	(b) (4)		
	2					2			
	3					3			
	4		Average	18		4		Average	59
	5		Std Dev	0.7		5		Std Dev	1.3
	6		RSD %	3.7		6		RSD %	2.1
	7		Maximum	(b) (4)		7		Maximum	(b) (4)
	8		Minimum			8		Minimum	
	9					9			
	10					10			
	11					11			
	12					12			
2 hour	1				10 hour	1			
	2					2			
	3					3			
	4		Average	29		4		Average	66
	5		Std Dev	0.6		5		Std Dev	1.4
	6		RSD %	2.2		6		RSD %	2.2
	7		Maximum	(b)		7		Maximum	(b) (4)
	8		Minimum	(4)		8		Minimum	
	9					9			
	10					10			
	11					11			
	12					12			
4 hour	1								
	2								
	3								
	4		Average	44					
	5		Std Dev	1.5					
	6		RSD %	3.4					
	7		Maximum	(b) (4)					
	8		Minimum						
	9								
	10								
	11								
	12								

Table 3.2.P.5.4.4.B: Raw Data for Dissolution release of Carbamazepine ER capsules 300 mg (B070068) using acetate buffer pH 4.5

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	Acetate buffer pH 4.5	900 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)		
	2			
	3			
	4		Average	17
	5		Std Dev	2.5
	6		RSD %	15.1
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
2 hour	1			
	2			
	3			
	4		Average	29
	5		Std Dev	1.6
	6		RSD %	5.5
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
4 hour	1			
	2			
	3			
	4		Average	45
	5		Std Dev	1.7
	6		RSD %	3.7
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
8 hour	1	(b) (4)		
	2			
	3			
	4		Average	62
	5		Std Dev	2.0
	6		RSD %	3.3
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
10 hour	1			
	2			
	3			
	4		Average	66
	5		Std Dev	1.7
	6		RSD %	2.7
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			

Table 3.2.P.5.4.4.C: Raw Data for Dissolution release of Carbamazepine ER capsules 300 mg (B070068) using phosphate buffer 6.8

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	Phosphate buffer pH 6.8	900 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)		
	2			
	3			
	4		Average	18
	5		Std Dev	0.5
	6		RSD %	2.6
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
2 hour	1			
	2			
	3			
	4		Average	28
	5		Std Dev	0.6
	6		RSD %	2.2
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
4 hour	1			
	2			
	3			
	4		Average	42
	5		Std Dev	1.1
	6		RSD %	2.5
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
8 hour	1	(b) (4)		
	2			
	3			
	4		Average	58
	5		Std Dev	0.9
	6		RSD %	1.6
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
10 hour	1			
	2			
	3			
	4		Average	62
	5		Std Dev	1.3
	6		RSD %	2.1
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			

Table 3.2.P.5.4.2.A: Raw Data for Dissolution release of Carbatrol® 300 mg (6N2897) using 0.1 N HCl

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	0.1 N HCl	900 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)		
	2			
	3			
	4		Average	21
	5		Std Dev	1.9
	6		RSD %	8.8
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
2 hour	1			
	2			
	3			
	4		Average	32
	5		Std Dev	2.8
	6		RSD %	9.0
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
4 hour	1			
	2			
	3			
	4		Average	43
	5		Std Dev	2.2
	6		RSD %	5.1
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
8 hour	1	(b) (4)		
	2			
	3			
	4		Average	53
	5		Std Dev	1.4
	6		RSD %	2.7
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
10 hour	1			
	2			
	3			
	4		Average	56
	5		Std Dev	1.5
	6		RSD %	2.8
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			

Table 3.2.P.5.4.2.B: Raw Data for Dissolution release of Carbatrol® 300 mg (6N2897) using acetate buffer pH 4.5

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	Acetate buffer pH 4.5	900 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)		
	2			
	3			
	4		Average	20
	5		Std Dev	0.6
	6		RSD %	2.7
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
2 hour	1			
	2			
	3			
	4		Average	29
	5		Std Dev	1.5
	6		RSD %	4.9
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
4 hour	1			
	2			
	3			
	4		Average	40
	5		Std Dev	1.7
	6		RSD %	4.2
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
8 hour	1	(b) (4)		
	2			
	3			
	4		Average	50
	5		Std Dev	0.8
	6		RSD %	1.6
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
10 hour	1			
	2			
	3			
	4		Average	52
	5		Std Dev	1.5
	6		RSD %	2.9
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			

Table 3.2.P.5.4.2.C: Raw Data for Dissolution release of Carbatrol® 300 mg (6N2897) using phosphate buffer 6.8

Apparatus	Speed	Temperature	Medium	Volume	Units tested
USP Apparatus 2 (paddle)	75 rpm	37° C	Phosphate buffer pH 6.8	900 mL	12

Sampling Time	Vessel	% Carbamazepine Released	Statistics	
1 hour	1	(b) (4)		
	2			
	3			
	4		Average	27
	5		Std Dev	1.2
	6		RSD %	4.6
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			
2 hour	1			
	2			
	3			
	4		Average	39
	5		Std Dev	1.2
	6		RSD %	3.0
	7		Maximum	(b)
	8		Minimum	(4)
	9			
	10			
	11			
	12			
4 hour	1			
	2			
	3			
	4		Average	52
	5		Std Dev	1.3
	6		RSD %	2.6
	7		Maximum	(b)
	8		Minimum	(4)
	9			
	10			
	11			
	12			
8 hour	1	(b) (4)		
	2			
	3			
	4		Average	61
	5		Std Dev	1.8
	6		RSD %	2.9
	7		Maximum	(b)
	8		Minimum	(4)
	9			
	10			
	11			
	12			
10 hour	1			
	2			
	3			
	4		Average	61
	5		Std Dev	1.9
	6		RSD %	3.2
	7		Maximum	(b) (4)
	8		Minimum	
	9			
	10			
	11			
	12			

4.1 Deficiency Comment

The firm should indicate if it accepts the following FDA-recommended dissolution method and specifications for its test product, Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg:

Apparatus:	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm
Medium	
First 4 hours:	Dilute acid, pH 1.1 with 1.8% β-cyclodextrin, 600 mL
After 4 hours:	50 mM Phosphate Buffer, pH 7.5 with 1.1% β-cyclodextrin, 1000 mL
Sampling Times	1, 2, 4, 8 and 10 hours
Specifications	**300 mg** strength: 1hr: (b) (4)%; 4 hr: (b) (4)%; 8 hr: NLT (b) (4)% **100 mg and 200 mg** strengths: 1hr: (b) (4)%; 4 hr: (b) (4)%; 8 hr: NLT (b) (4)%

4.2 Recommendation

1. The Division of Bioequivalence accepts the fasting BE study (0710050) conducted by Nostrum on its Carbamazepine ER capsules, 300 mg (Lot # G070068B) comparing it to Shire's Carbatrol® 300 mg Capsules (lot #6N2897).

2. The Division of Bioequivalence accepts the fed BE study (0712061) conducted by Nostrum on its Carbamazepine ER capsules, 300 mg (Lot # G070068B) comparing it to Shire's Carbatrol® 300 mg Capsules (lot #6N2897).

3. The Division of Bioequivalence accepts the sprinkle BE study (0712062) conducted by the Nostrum on its Carbamazepine ER capsules, 300 mg (Lot # G070068B) comparing it to Shire's Carbatrol® 300 mg Capsules (lot #6N2897).

4. The firm's *in vitro* dissolution testing is incomplete pending its acceptance and acknowledgment of the FDA-recommended dissolution method and specifications. The dissolution testing should be conducted using the following dissolution method and the test product should meet the indicated specifications:

Apparatus:	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm
Medium	
First 4 hours:	Dilute acid, pH 1.1 with 1.8% β-cyclodextrin, 600 mL
After 4 hours:	50 mM Phosphate Buffer, pH 7.5 with 1.1%

	β-cyclodextrin, 1000 mL
Sampling Times	1, 2, 4, 8 and 10 hours
Specifications	**300 mg** strength: 1hr: (b) (4) %; 4 hr: (b) (4) %; 8 hr: NLT (b) (4) % **100 mg and 200 mg** strengths: 1hr: (b) (4) %; 4 hr: (b) (4) %; 8 hr: NLT (b) (4) %

4.3 Comments for Other OGD Disciplines

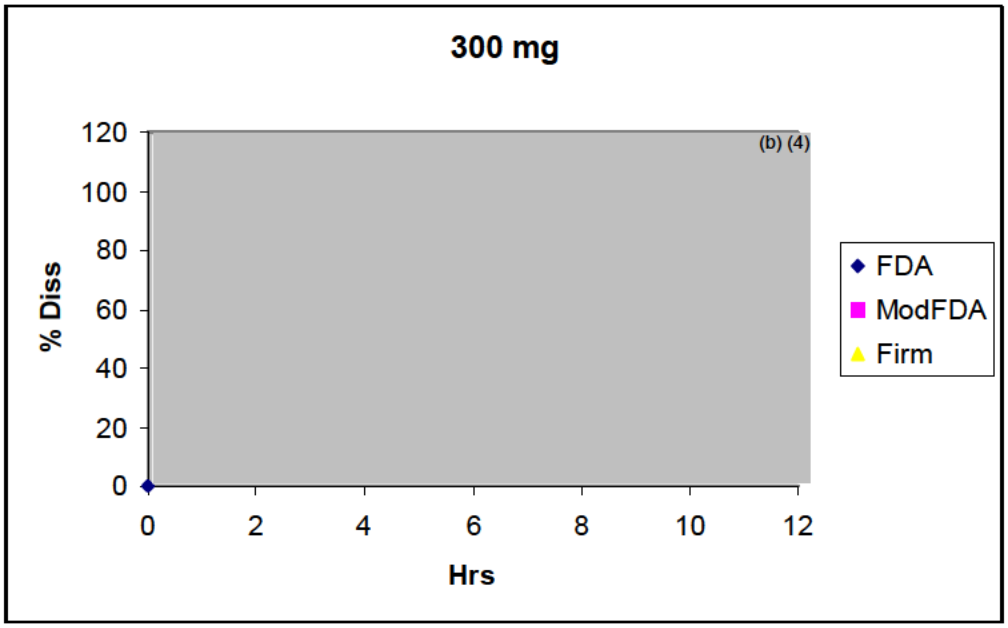
Discipline	Comment
N/A	

4.4 Additional Attachments

Dissolution Consultation (Dr. Paul Seo)

Hi Kim,

Here's a quick plot of the 300mg test data:



Based on this, I would lean towards the original FDA method in that it provides adequate dissolution while maintaining good discrimination. You lose one or the other if you go w/ the firm's method or modified FDA method. Nostrum is probably trying to make their lives easier by having a single media test. So at this point, I would suggest getting data on the other strengths using the FDA method, and then set final specs for all strengths then (ie dont tell them your recommended specs yet).

Hope this helps,
Paul

From: Raines, Kimberly
Sent: Tuesday, September 30, 2008 10:38 AM
To: Seo, Paul
Cc: Dhariwal, Kuldeep R
Subject: Dissolution Consultation ANDA 76697 (Nostrum) Carbamazepine ER Cap, 100 mg, 200 mg and 300 mg

Hi Paul,

The firm has submitted comparison dissolution testing for the test and reference drug products using the following dissolution methods…. (1) FDA-recommended method (as listed on the website); (2) modified FDA-recommended method (same media; without pH change); (3) Firm's proposed dissolution method (0.1% SLS pH 1.2). Please see summary tables below (individual capsule data is also available).

(1a) FDA-recommended Method (Test Products)
<< OLE Object: Picture (Enhanced Metafile) >>

(1b) FDA-recommended Method (RLD)
<< OLE Object: Picture (Enhanced Metafile) >>
(2) FDA-method without pH change (Test Product)
<< OLE Object: Picture (Enhanced Metafile) >>
(3) Firm's proposed method (0.1 SLS%, pH 1.2)
<< OLE Object: Picture (Enhanced Metafile) >>

Which method do you feel is most discriminatory and should be recommended to the firm?

In my opinion, the firm's proposed method is not reasonable because at least 80% dissolution is not achieved for either the test or reference products. In the case of the modified FDA-method without pH change, the firm would meet the specifications indicated on the internal Dissolution Database 1hr: (b) (4)%; 4 hr: (b) (4)%; 8 hr: NLT (b) (4)% (300 mg strength meets at L1; would need to request additional dissolution testing on the 100 mg and 200 mg strengths). If we would like to remain consistent we can request that the firm complete dissolution testing using the FDA-recommend and suggest the following specifications for the firm…. 300 mg strength 1hr: (b) (4)%; 4 hr: (b) (4)%; 8 hr: NLT (b) (4)% (firm meets at L2) 100 mg and 200 mg strengths 1 hr: (b) (4)%; 4 hr: (b) (4)%; 8 hr: NLT (b) (4)% (firm meets at L1). I appreciate your feedback, if you need any additional data please let me know (I didn't want all of the raw data to clog your email). Thank you.

Kimberly W. Raines, Ph.D.
Pharmacologist
Division of Bioequivalence
Office of Generic Drugs
CDER/FDA
MPN 1 Rm. 1323
Tel: 240-276-8762
Fax: 240-276-8766
kimberly.raines@fda.hhs.gov

Email from Firm Representative

From: Dhiren Shah [mailto:dshah@nostrumlabs.com]
Sent: Wednesday, September 24, 2008 12:22 PM
To: Thompson, Christina
Cc: Zoia Ploscaru
Subject: Carbamazepine ER Capsules -- ANDA 76-697

Hello Christina:

I am just following up on our phone conversation today.

You requested Nostrum to provide dissolution data on the RLD (all three strengths) in (i) FDA recommended method (cyclodextrin), and (ii) 0.1% SLS method. Also, you advised Nostrum that it should provide (i) detailed description of all the dissolution methods employed for the drug product and (ii) a justification for using the 0.1% SLS dissolution method.

Nostrum will follow-up of on the above requests (as well as earlier request made last week) and submit an amendment very soon.

On an administrative matter, please note that Ms. Zoia Ploscaru has joined Nostrum as the head of regulatory affairs and she will be in touch with you in the future.

Thank you and best regards.

Dhiren

Dhiren N. Shah, Ph.D., RAC
Regulatory Affairs Consultant
Nostrum Laboratories, Inc.,
1800 N. Topping Ave.,
Kansas City, MO 64120-3510
Tel: (816) 308-4970
Fax: (816) 308-4975
Cell: (b) (6)
e-mail: dshah@nostrumlabs.com

Bio Management Meeting Minutes 09-22-08

Discussion Topic: ANDA # Carbamazepine ER Capsules 300 mg, 200 mg and 100 mg (Nostrum)-Presented by Kimberly Raines

In response to a previous bioequivalence deficiency the firm submitted dissolution testing data utilizing the FDA-recommended method on all strengths of the test product and additional dissolution testing on the highest strength of the test product in pH 1.2, pH 4.5 and pH 6.8 buffers. The firm did not provide dissolution testing on the reference listed product; therefore comparative dissolution could not be evaluated by the reviewer. A telephone amendment was issued to the firm in which they were asked to **(1)** conduct dissolution testing on all three strengths of the reference product using the FDA-recommended method and **(2)** conduct dissolution testing on the highest strength of the reference product in three additional media, pH 1.2, pH 4.5 and pH 6.8.

The firm responded to the telephone amendment by sending an email correspondence (see below).

FW ANDA 76-697 -- Additional Dissolution

Question: Should we have the firm complete dissolution testing of the reference product using the FDA-recommended method as well as their suggested method?

Management Discussion:

Have the firm complete dissolution testing using both the FDA-recommended method and their recommended method (0.1% SLS) for all strengths the reference product. Also ask to the firm to justify/explain the reasoning behind their suggested methodology. In

addition the firm is still required to submit dissolution testing of the highest strength of the reference product in three additional media (pH 1.2, pH 4.5 and pH 6.8). Review all data before making a recommendation on final method and specification.

BIOEQUIVALENCE DEFICIENCY

ANDA: 76697

APPLICANT: Nostrum Pharmaceuticals LLC

DRUG PRODUCT: Carbamazepine Extended-Release Capsules 100 mg, 200 mg and 300 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Based on the submitted data, DBE recommends the following dissolution method and specifications for your test product:

Apparatus:	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm
Medium	
First 4 hours:	Dilute acid, pH 1.1 with 1.8% β-cyclodextrin, 600 mL
After 4 hours:	50 mM Phosphate Buffer, pH 7.5 with 1.1% β-cyclodextrin, 1000 mL
Sampling Times	1, 2, 4, 8 and 10 hours
Specifications	**300 mg** strength: 1hr: (b) (4)%; 4 hr: (b) (4)%; 8 hr: NLT (b) (4)% **100 mg and 200 mg** strengths: 1hr: (b) (4)%; 4 hr: (b) (4)%; 8 hr: NLT (b) (4)%

With your response, please indicate if you accept the above FDA-recommended dissolution method and specifications.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

ANDA: 76697

Completed Assignment for 76697 ID: 6617

Reviewer: Raines, Kimberly **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6617	9/3/2008	Other	Study Amendment	1	1
6617	9/25/2008	Other	Study Amendment	1	1
				Bean Total:	2

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment (s)	
Study Amendment long term stability	0
Study Amendment Dissolution data new/resubmitted	2
Study Amendment Total	*2*

Grand Total	**2**

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

/s/

Kimberly W Raines
10/14/2008 08:50:29 AM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
10/14/2008 09:13:43 AM
BIOPHARMACEUTICS

Moheb H. Makary
10/14/2008 09:46:08 AM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	76-697
Drug Product Name	Carbamazepine Extended-Release Capsules
Strength	100 mg, 200 mg, and 300 mg
Applicant Name	Nostrum Pharmaceuticals, LLC
Submission Date	11/24/2008
Reviewer	Aaron Sigler, Pharm.D.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The bioequivalence section of the application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing. The bioequivalence section of the application is acceptable.

Enter Review Productivity and Generate Report

http://cdsogd1/bioprod

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

/s/

Aaron Sigler
12/3/2008 02:36:11 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76697		
Drug Product Name	Carbamazepine Extended Release Capsules		
Strength(s)	100 mg, 200 mg, and 300 mg		
Applicant Name	Nostrum Pharmaceuticals Inc.		
Address	505 Thornall Street Edison, NJ 08837		
Applicant's Point of Contact	Dhiren N. Shah, Ph.D., RAC		
Contact's Telephone Number	816-308-4970		
Contact's Fax Number	816-841-4634		
Original Submission Date(s)	March 26, 2003		
Submission Date(s) of Amendment(s) Under Review	April 28, 2008		
Reviewer	Kimberly W. Raines		
Study Number (s)	0710050	0712061	0712062
Study Type (s)	Fasting	Fed	Fasting Sprinkle
Strength (s)	300 mg	300 mg	300 mg
Clinical Site	RelClin, Reliance Clinical Pharmacology and Pharmacokinetic Facility		
Clinical Site Address	Rabale, Navi Mumbai, India		
Analytical Site	(b) (4)		
Analytical Site Address			
OUTCOME DECISION	**ACCEPTABLE**		

Review of Bioequivalence Studies for Tmax differences

1 EXECUTIVE SUMMARY

Carbatrol® (carbamazepine) extended-release capsules (NDA 20-712) were approved in 1997 as an anticonvulsant and specific analgesic for trigeminal neuralgia. Carbatrol® is formulated as a capsule consisting of immediate release, extended release, and enteric release beads. Recent attention has shed light on possible differences in Tmax values between generic formulations of carbamazepine extended-release capsules and reference listed drug (RLD). It is suggested that significant differences in Tmax may render generic products not therapeutically equivalent to the RLD.

At the request of the Division of Chemistry 3, the Division of Bioequivalence (DBE) 2 investigated possible Tmax differences between Nostrum's Carbamazepine Extended Release Capsules, 300 mg and the RLD, Carbatrol®, ER Capsules 300 mg, manufactured by Shire US. The DBE 2 reviewed Tmax values obtained in the fasting, fed, and fasting

sprinkle *in vivo* bioequivalence (BE) studies submitted by Nostrum on April 28, 2008 in ANDA #76697.

Upon review it was determined that for the fasting and fasting sprinkle BE studies, the test product Tmax median values are not significantly different from the Tmax of the RLD, demonstrating a T/R ratio of 1.04 and 1.08, respectively. It is also noted that the mean plasma concentration curves of the test and reference products are almost super imposable for the fasting and fasting sprinkle BE studies.

In the fed BE study, the median Tmax does appear to be different than that of the RLD, 21 hours for the test and 14 hours for the reference product. The T/R ratio for the fed BE study is 1.50. In the fed BE study 8 subjects (N=21) demonstrated significantly different (> 8 hr) Tmax values between the test and reference products.

The RLD label[1] states, "A high fat meal diet increased the rate of absorption of a single 400 mg dose (mean T_{max} was reduced from 24 hours, in the fasting state, to 14 hours and C_{max} increased from 3.2 to 4.3 µg/mL) but not the extent (AUC) of absorption. Carbatrol® can be taken with or without meals."

Therefore the DBE 2 does not consider the difference in median Tmax values between the test product and RLD in the fed BE study to be of clinical significance, as the Tmax values fall within the limits set forth in the label.

It should be noted that the test product, Nostrum's Carbamazepine Extended-Release Capsules, do not demonstrate a food effect (i.e. a significant reduction in Tmax under fed conditions), as indicated in the RLD label and demonstrated in the submitted *in vivo* bioequivalence studies. The Labeling Division should be aware of this matter, as the Nostrum product could not support the RLD label.

The application is complete. A letter to the firm is not needed.

[1] http://www.fda.gov/cder/foi/label/2007/020712s029lbl.pdf (Approved 12/2007)

2 TABLE OF CONTENTS

3 SUMMARY REVIEW

3.1 Drug Product Information

Test Product	Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg
Reference Product	Carbatrol® (carbamazepine) extended-release capsules, 300 mg
RLD Manufacturer	Shire US
NDA No.	20-712
RLD Approval Date	September 30, 1997
Indication	Anticonvulsant

Excerpts from the Carbatrol® label[2]

Taken every 12 hours, carbamazepine extended-release capsules provide steady state plasma levels comparable to immediate-release carbamazepine tablets given every 6 hours, when administered at the same total mg daily dose.

Following a single 200 mg oral extended-release dose of carbamazepine, **peak plasma concentration was 1.9 ± 0.3 µg/mL and the time to reach the peak was 19 ± 7 hours** (12-26 hrs).

A high fat meal diet increased the rate of absorption of a single 400 mg dose (**mean T_{max} was reduced from 24 hours, in the fasting state, to 14 hours** and C_{max} increased from 3.2 to 4.3 µg/mL) but not the extent (AUC) of absorption.

The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

The Carbatrol® capsules may be opened and the beads sprinkled over food, such as a teaspoon of applesauce or other similar food products if this method of administration is preferred. Carbatrol® capsules or their contents should not be crushed or chewed. **Carbatrol® can be taken with or without meals.**

[2] http://www.fda.gov/cder/foi/label/2007/020712s029lbl.pdf (Approved 12/2007)

3.2 Tmax Review

Fasting Study

Carbamazepine 300 mg
Fasting Bioequivalence Study No. 0710050, N= 22*
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

	carbamazepine				
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	209938.0	222505.0	0.94	87.66	101.56
AUC∞ (ng·hr/mL)	224511.8	239890.9	0.94	87.23	100.41
Cmax (ng/mL)	2172.50	2262.23	0.96	88.63	104.06

Fasting Bioequivalence Study, Study No. 0710050
Carbamazepine*

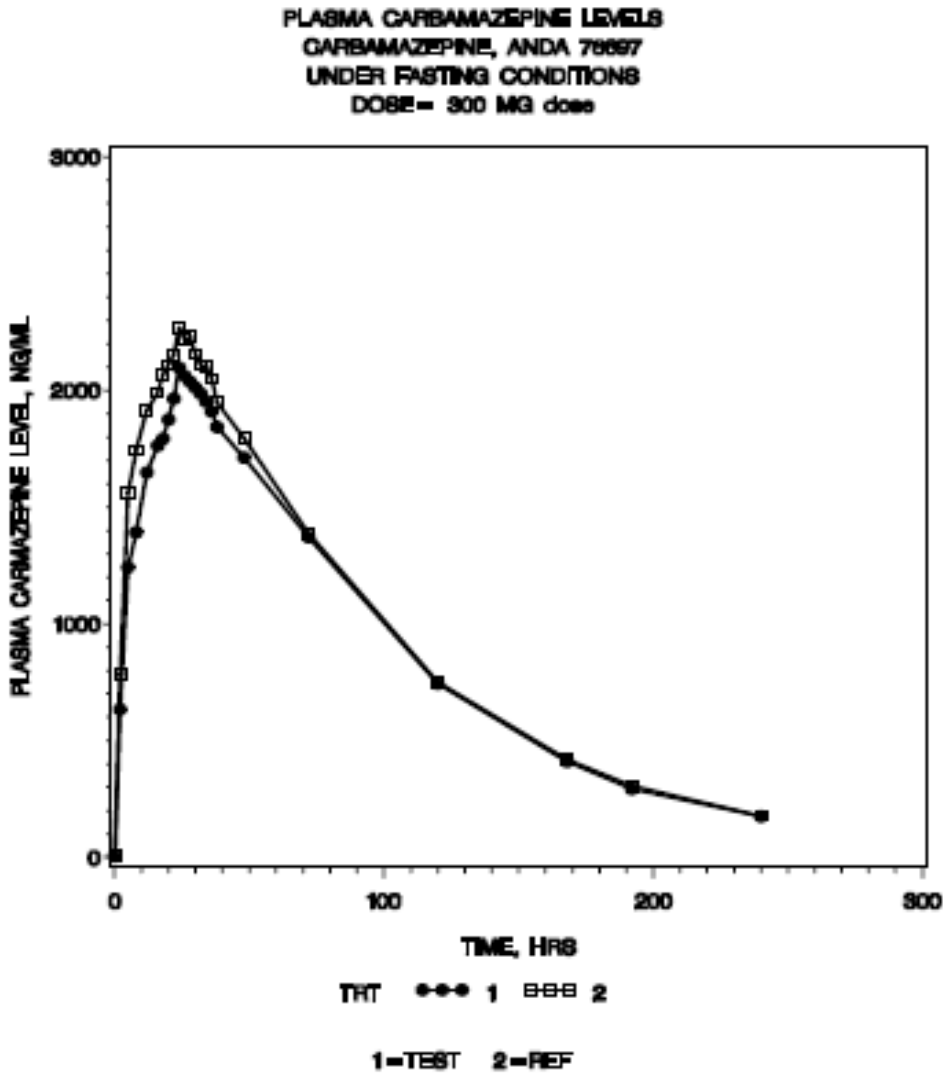
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
AUC0-t (hr *ng/ml)	214933.6	21.58	145810.6	331748.7	226191.1	20.25	152289.0	311756.2	0.95
AUC∞ (hr *ng/ml)	230053.4	22.19	149390.2	345647.8	244443.3	21.99	154944.2	356783.9	0.94
Cmax (ng/ml)	2210.163	17.13	1504.04	3001.58	2287.791	17.56	1340.22	2847.99	0.97
Tmax* (hr)	25.035	.	12.00	36.00	24.000	.	12.00	32.00	1.04
Kel (hr^{-1})	0.013	23.89	0.01	0.02	0.013	23.13	0.01	0.02	1.01
T1/2 (hr)	57.562	24.11	37.80	89.63	59.286	31.80	37.62	122.69	0.97

*The original reviewer of this ANDA calculated the median Tmax value for N=22, excluding subjects 1 and 7, as per protocol. (Test: 25.035 hrs (range 12-36 hrs); Reference: 24 hrs (range 12-32 hrs). Upon review of the originally calculated median Tmax values, the current reviewer is in agreement with the median Tmax values, but identified different Tmax ranges for the test and reference products when evaluating the raw data (Test range: 18-34 hrs; Reference range: 12-36 hrs).

Subject	Test	Reference
2	24	24
3	24	12
4	24.07	22
5	18	26
6	34	24
8	32	24
9	22	24
10	26	28
11	30	24
12	22	12
13	24	24

14	26	24
15	24	24
16	18	30
17	22	18
18	28	24
19	28	28
21	32	36
22	28	28
23	28	26
24	24	28
25	30	24
MEAN	25.82136	24.27273
Median	*25.035*	*24*

Test	**Reference**
18	12
18	12
22	18
22	22
22	24
24	24
24	24
24	24
24	24
24	24
24.07	24
26	24
26	24
28	24
28	26
28	26
28	28
30	28
30	28
32	28
32	30
34	36



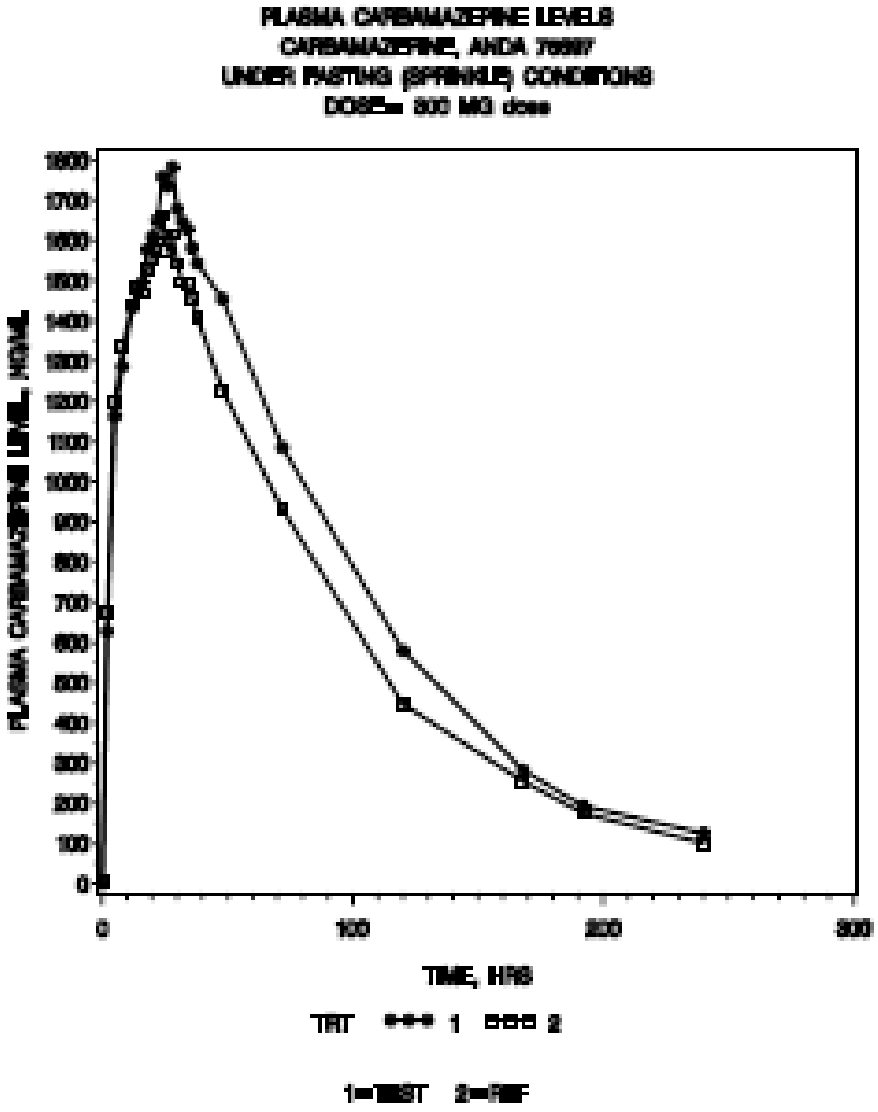
Reviewer's Comment:

The difference between Tmax for the test product and RLD is not significant.

Sprinkle Fasting Study

Carbamazepine 300 mg Fasting Sprinkle Bioequivalence Study No. 0710062, N= 24 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
	carbamazepine				
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	153180.1	168673.0	0.91	85.36	96.62
AUC∞ (ng·hr/mL)	161477.4	177183.9	0.91	85.57	97.07
Cmax (ng/mL)	1667.70	1896.23	0.88	82.72	93.51

Fasting (Sprinkle) Bioequivalence Study, Study No. 0712062									
	Carbamazepine								
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	157760.2	24.70	88351.92	244866.3	172284.7	22.08	128860.8	258780.5	0.92
AUC∞ (hr *ng/ml)	167121.3	26.81	90280.47	274141.0	182095.1	25.45	132787.6	293880.0	0.92
Cmax (ng/ml)	1691.634	16.99	1101.64	2253.60	1919.766	15.97	1396.67	2673.02	0.88
Tmax* (hr)	26.000	.	12.00	38.00	24.000	.	8.00	38.00	1.08
Kel (hr^{-1})	0.014	22.78	0.01	0.02	0.014	19.97	0.01	0.02	1.01
T1/2 (hr)	51.897	23.82	33.20	85.98	52.109	22.22	37.67	84.53	1.00



Reviewer's Comment:

The current reviewer is in agreement with the original reviewer's calculations of median Tmax and the Tmax range for the test and reference products for the fed bioequivalence study. The difference between Tmax for the test product and RLD is not significant.

Fed Study

Carbamazepine 300 mg Fed Bioequivalence Study No. 0710061, N= 22 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
	carbamazepine				
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	203184.1	227368.7	0.89	82.59	96.69
AUC∞ (ng·hr/mL)	222576.3	240932.7	0.92	87.55	97.48
Cmax (ng/mL)	2395.60	2644.59	0.91	86.75	94.58

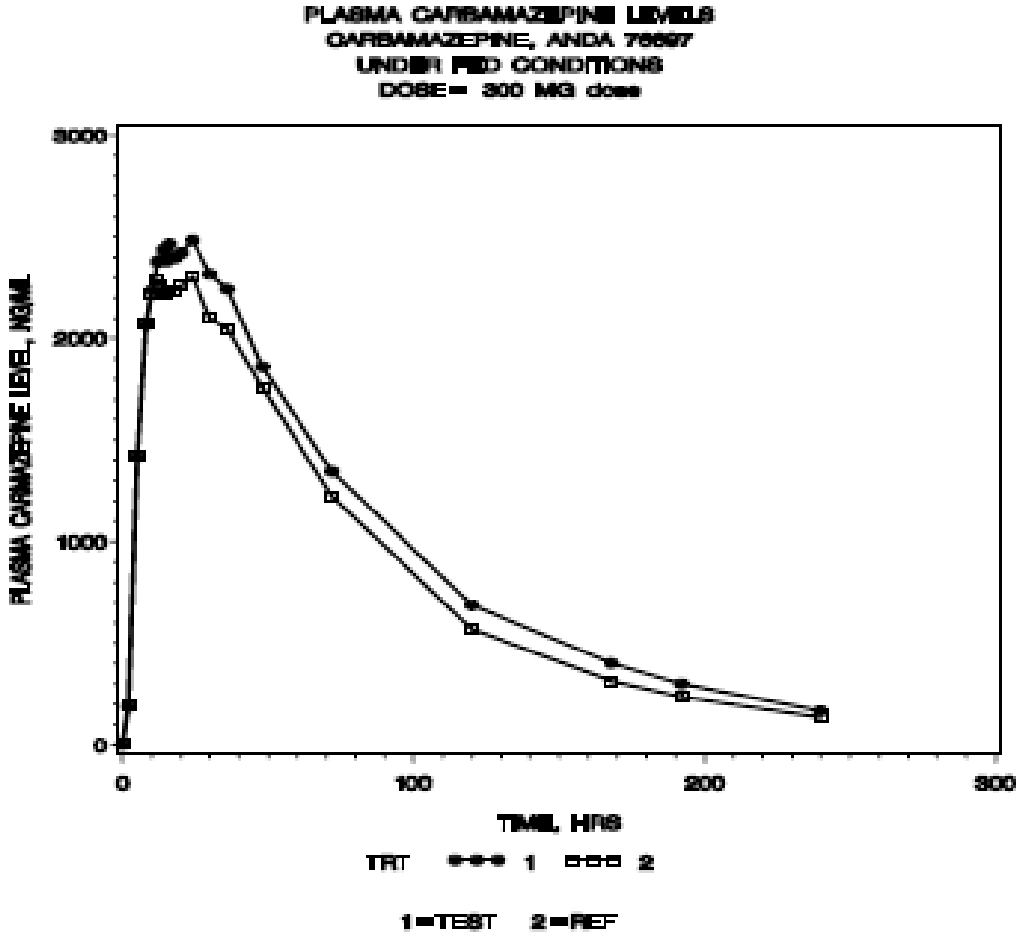
Fed Bioequivalence Study, Study No. 712061 Carbamazepine									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	205282.8	19.13	125672.7	283104.9	232360.6	19.37	163515.5	323524.2	0.88
AUC∞ (hr *ng/ml)	226478.6	22.27	154380.1	357373.5	248442.0	24.38	164796.2	396305.7	0.91
Cmax (ng/ml)	2418.886	16.67	1858.20	3444.78	2670.072	12.57	2243.40	3415.75	0.91
Tmax* (hr)	21.000	.	12.00	36.00	14.000	.	10.00	24.00	1.50
Kel (hr^{-1})	0.014	22.46	0.01	0.02	0.014	24.65	0.01	0.02	1.03
T1/2 (hr)	52.080	23.65	35.07	83.06	54.082	28.92	34.25	99.63	0.96

Excerpt from ANDA 76697 Amendment Review April 28, 2008[3]

Reviewers Comments:

For the test product, there is about 20% decrease in Tmax under fed conditions (vs. fasting conditions). For the reference product, there was about 40% decrease in Tmax under fed conditions (vs. fasting conditions). No appreciable difference in the median Tmax values between the test and reference products was observed in the fasting and sprinkle studies. Since according to the RLD labeling, "Carbatrol® can be taken with or without meals," the difference in median Tmax values between the test and reference may not have any clinical significance.

[3] DFS N076697 N 000 AC 28-Apr-2008


PLASMA CARBAMAZEPINE LEVELS
CARBAMAZEPINE, ANDA 76697
UNDER FED CONDITIONS
DOSE= 300 MG dose
PLASMA CARBAMAZEPINE LEVEL, NG/ML
3000
2000
1000
0
0
100
200
300
TIME, HRS
TRT 1 2
1=TEST 2=REF

Individual Tmax Values

Subject	Test	Fed Tmax Reference
1	12	12
2	14	14
3	24	15
4	36	12
6	18	14
7	14	18
8	18	24
9	18	14
10	30	13
11	13	18
12	13	13
13	24	12
14	30	14
16	13	24
18	24	13
19	16	24
20	24	24
21	24	14
23	16	12
24	30	24
25	24	10
26	24	20

Calculation of Median Tmax (Reviewer Calculated)
(Test: 21 hrs (range: 12-36 hrs); Reference: 14 hrs (range 10-24 hrs))

12	10
13	12
13	12
13	12
14	12
14	13
16	13
16	13
18	14
18	14
18	14
24	14
24	14
24	15
24	18
24	18
24	20
24	24
30	24

	30	24
	30	24
	36	24
MEAN	**20.86364**	**16.27273**
Median	**21**	**14**

Reviewer's Comment:

The reviewer is in agreement with the previous reviewer. As the label states, Carbatrol® can be taken without regard to meals. The Tmax difference between the test product and RLD is within the limits stated in the label; therefore the difference in Tmax is not significant.

3.3 Outcome Page

ANDA: 76697

Completed Assignment for 76697 ID: 7956

Reviewer: Raines, Kimberly **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7956	4/28/2008	Other	Study Amendment	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment (s)	
Study Amendment	1
Study Amendment Total	*1*

Grand Total	**1**

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

/s/

Kimberly W Raines
4/28/2009 03:27:56 PM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
4/28/2009 03:30:17 PM
BIOPHARMACEUTICS

Barbara Davit
4/30/2009 03:12:56 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-697

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MARTEC
SCIENTIFIC, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

Refuse to receive.
14-MAY-2003

March 26, 2003

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – RM 150
7500 Standish Place
Rockville, MD 20855-2773

ANDA submission for Carbamazepine Extended-Release Capsules, 300 mg

Dear Mr. Buehler:

In accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act, Nostrum Pharmaceuticals, Inc., 203 Somerset Ct. Princeton, NJ 08450 is submitting an Abbreviated New Drug Application for Carbamzepine Extended-Release Capsules, 300 mg through its authorized agent Paul T. Sudhakar, President/CEO of Martec Scientific. The Archival and the Review copies contain 9 volumes each (4 for the Chemistry, Manufacturing and Controls section and 5 for the Pharmacokinetics section). A field copy of the entire Chemistry, Manufacturing and Controls section has been forwarded to the Kansas City, Field Office, with the required certification that it is an exact true copy of the Archival copy.

The complete pharmacokinetics study report (5 volumes) consists of five studies presented in the following order:

1. **Single dose fasted study** Vs Carbatrol ® (Shire) – Study number PRACS R02-733.

2. **Single dose food** effect study Vs Carbatrol ® (Shire) ® – Study number PRACS R02-734

Diskettes with the raw data files are provided for each of the studies

Three copies of the analytical methods and the methods validation package are also included.

Sincerely,

Paul T. Sudhakar
President/CEO
Martec Scientific, Inc
Agent for Nostrum Pharmaceuticals, Inc.

Tel: 816-241-4144
800-822-6782
Fax: 816-483-5432

Enclosures

1. **Archival copy of CMC (4 volumes)**
2. **Review copy of CMC (4 volumes)**
3. **Archival copy of pharmacokinetics (5 volumes)**
4. **Review copy of pharmacokinetics (5 volumes)**
5. **2 Floppy diskettes for each copy of the pharmacokinetics**
6. **3 copies of analytical methods and methods validation package**

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

March 12, 2003

Mr. Gary J. Buehler
Director
Office of Generic Drugs
Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Re: Abbreviated New Drug Application (ANDA)
Carbamazepine Extended-release capsules, 300 mg

Dear Mr. Buehler:

Please accept this letter as authorization for Paul T, Sudhakar, President/CEO Martec Scientific, Inc., Kansas City, MO to act as its agent for Nostrum Pharmaceuticals, Inc. with respect to the aforementioned ANDA submission and regulatory processes. All correspondence related to this ANDA submission and review process should be directed to him.

Address: Martec Scientific, Inc.
1800 N. Topping Avenue
P.O. Box 33510
Kansas City, MO 64120

Tel: 816-241-4144 or 1-800-822-6782
Fax: 816-483-5432 or 1-800-287-7576

Should you have any questions or comments, please do not hesitate to contact the undersigned at (732) 355-1411 or Paul Sudhakar at (800) 822-6782.

Sincerely,

Nirmal Mulye, Ph.D.
President/CEO

c.c. Paul Sudhakar, President/CEO, Martec Scientific, Inc.

Bio

MEMORANDUM

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

DATE : April 3, 2003

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 03-APR-2003

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Carbamazepine Extended-release Capsules, 300 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j)(5)(B)(iv).

Nostrum Pharmaceuticals, Inc. has submitted ANDA 76-697 for Carbamazepine Extended-release Capsules, 300 mg . The ANDA contains a certification pursuant to 21 USC 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Nostrum Pharmaceuticals, Inc. on March 26, 2003 for its Carbamazepine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 76697 **FIRM NAME** **Nostrum Pharmaceuticals, Inc., c/o Martec Scientific, Inc.**

DRUG NAME Carbamazepine

DOSAGE FORM **Extended-Release Capsule, 300 mg**
SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

Lin-Whei Chuang Date: 4/9/2003
Reviewer

Yih-Chain Huang Date: 4/11/2003
Team Leader

Dale Conner Date: 4/14/2003
Director, Division of Bioequivalence

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			
Assay Methodology	☒	☐			
Procedure SOP	☒	☐			
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			
Adverse Events	☒	☐			
IRB Approval	☒	☐			
Dissolution Data	☒	☐			
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			
Consent Forms	☒	☐			
Composition	☒	☐			
Summary of Study	☒	☐			
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted)	☒	☐			
Randomization Schedule	☒	☐			
Protocol Deviations	☒	☐			
Clinical Site	☒	☐			
Analytical Site	☒	☐			
Study Investigators	☒	☐			
Medical Records	☒	☐			

Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☒	☐			
BIO Batch Size	☐	☒			
Assay of Active Content Drug	☒	☐			
Content Uniformity	☒	☐			
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐			
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☐	☒			

Additional Comments regarding the ANDA:
The submission contains a fasting and a non-fasting BE studies.

ANDA 76-697 Final Check List for Branch Chief RTR

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for gross errors in letter.

✓ 3) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 4) Check address and contact person on letter vs. 356(h).

✓ 5) Check for any t-cons and verify date and correspondence date.

✓ 6) Check Patent Certification information in entered in COMIS (by Margo) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 7) Check for any comments or problems raised by reviewer on Check List.

✓ 8) Sign Check List.

✓ 9) Check electronic Orange Book to verify current patent information.

✓ 10) Review 356 (h). Check NDA number and RLD for correct reference.

✓ 11) Review Basis for Submission.

✓ 12) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 13) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 14) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 15) Pull USP information. (USP ____yes ✓ no)

✓ 16) Final Grammar review on letter.

____ 17) EES slip.

____ 18) Document in record book.

Signature [signature] date 5/9/13

ANDA 76-697 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for gross errors in letter.

✓ 3) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 4) Check address and contact person on letter vs. 356(h).

✓ 5) Check for any t-cons and verify date and correspondence date.

✓ 6) Check Patent Certification information in entered in COMIS (by Margo) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 7) Check for any comments or problems raised by reviewer on Check List. Addressed in Response to RPT

✓ 8) Sign Check List.

✓ 9) Check electronic Orange Book to verify current patent information.

✓ 10) Review 356 (h). Check NDA number and RLD for correct reference.

✓ 11) Review Basis for Submission.

✓ 12) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 13) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 14) Sign cover letter 505 (J)(2)(A) OK, date, and full signature.

✓ 15) Pull USP information. (USP ____yes ✓ no)

_____ 16) Final Grammar review on letter.

_____ 17) EES slip.

_____ 18) Document in record book.

Signature_____ date_____

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA#: 76-697 **FIRM NAME** NOSTRUM PHARMACETICALS, INC.

RELATED APPLICATION(S): NA **First Generic Product Received?** YES

DRUG NAME: CARBAMAZEPINE
DOSAGE FORM: EXTENDED-RELEASE CAPSULES

Random Queue: Random 10 Chem Team Leader: Rosencrance, Susan PM: Ho, Sarah

Labeling Reviewer: Dillahunt, Michelle Micro Review: NA Clinical Review: NA

Letter Date MARCH 26, 2003	**Received Date** MARCH 28, 2003
Comments EC-1 YES **On Cards YES** **ANTICONVULSANTS**	**Therapeutic Code 2010300**
Methods Validation Package (3 copies) (Required for Non-USP drugs) YES	(Not Applicable to Electronically Archived Submissions)
Archival and Review copies Field Copy Certification (Original Signature) NOT ORGINAL SIGNATURE SUBMITTED	(Not Applicable to Electronically Archived Submissions)
Cover Letter YES X	**Table of Contents YES** X
PART 3 Combination Product Category X Unknown (Must be completedfor ALL Original Applications)	Refer to the Part 3 Combination Algorithm

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) RX YES Paul T. Sudhakar 816-241-4144	☒
Sec. II	**Basis for Submission** **NDA: 20-712** RLD: CARBATROL Firm: SHIRE ANDA suitability petition required? If yes, consult needed for pediatric study requirement.	☒
Sec. III	**Patent Certification** 1. Paragraph: IV 2. Expiration of Patent: JUN-15-2016 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement YES**	☒

Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) **2. Request for Waiver of In-Vivo Study(ies):** N/A **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) N/A **4. Lot Numbers of Products used in BE Study(ies):** ✓ **5. Study Type:** (Continue with the appropriate study type box below)	☐
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 300 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) fast - p189 ✓ fed p202 ✓ by point estimate b. Data Files (Computer Media) Submitted YES SENT TO CDR c. In-Vitro Dissolution UNKNOWN p233 ✓ Biokay according to first generic review	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted	N/A
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. Data Files (Computer Media) Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	N/A

lot # - 020313

(b) (4) → (b) (4) caps

caps

(b) (4)

caps

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☒ N/A
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐ N/A
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation 2. Inactive ingredients as appropriate	☐
Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis c. COA(s) specifications and test results from drug substance mfgr(s) ✓ d. Applicant certificate of analysis – from maitec – is maitec drug product manufacturer e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified ✓ b. Testing specifications (including identification and characterization) ✓ c. Suppliers' COA (specifications and test results) ✓ d. Applicant certificate of analysis ✓	☒
Sec.IX	**Description of Manufacturing Facility** Maitec 1. Full Address(es)of the Facility(ies) ✓ 2. CGMP Certification YES pass ✓ 3. CFN numbers	☒

Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including MicrobiologicalValidation, if Appropriate) 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement p 1049	
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 2. In-process Controls - Specifications and data	
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) 2. Components Specification and Test Data (Type III DMF References) 3. Packaging Configuration and Sizes 4. Container/Closure Testing 5. Source of supply and suppliers address	
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data 2. Certificate of Analysis for Finished Dosage Form	
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted 2. Post Approval Commitments 3. Expiration Dating Period 4. Stability Data Submitted a. 3 month accelerated stability data b. Batch numbers on stability records the same as the test batch	
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	
Sec. XVII	**Environmental Impact Analysis Statement**	

Sec. XVIII	GDEA (Generic Drug Enforcement Act)/Other: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) p 1781 2. Debarment Certification (original signature) YES p1805 3. List of Convictions statement (original signature)	☐

Reviewing CSO/CST Emily Monica Date 5/1/03	Recommendation: ☐ FILE ☒ REFUSE to RECEIVE
Supervisory Concurrence/Date: [signature]	**Date:** 5/9/03
Duplicate copy sent to bio: (Hold if RF and send when acceptable)	
Duplicate copy to **HFD-** for consult: Type:	

ADDITIONAL COMMENTS REGARDING THE ANDA:

✓ fix established name on 356h and check ANDA box ; and Shire Pharm
✓ need financial cert form a disclosure form for Bio study for Approved App Holder
✓ need DMF authorization letter from (b) (4) or
letter authorizing (b) (4) to act on their behalf
✓ need (b) (4) too high
✓ need GDEA from Nostrum
✓ need LOA from Nostrum w/ orig sig
✓ need field copy w/ orig sig

OGD Template Revised 04/01/2003

Martec ANDA 76-697 Final Check List for Branch Chief Refuse to Receive

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for gross errors in letter.

___ 3) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 4) Check address and contact person on letter vs. 356(h).

✓ 5) Check for any t-cons and verify date and correspondence date.

✓ 6) Check Patent Certification information in entered in COMIS (by Margo) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 7) Check for any comments or problems raised by reviewer on Check List.

✓ 8) Sign Check List.

✓ 9) Check electronic Orange Book to verify current patent information.

✓ 10) Review 356 (h). Check NDA number and RLD for correct reference.

✓ 11) Review Basis for Submission.

✓ 12) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 13) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 14) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 15) Pull USP information. (USP ___yes ✓ no)

✓ 16) Final Grammar review on letter.

___ 17) EES slip.

___ 18) Document in record book.

Signature [signature] date 5/13/23

ANDA 76-697

Martec Scientific, Inc.
U.S. Agent for Nostrum Pharmaceuticals, Inc.
Attention: Paul T. Sudhakar
1800 N. Topping Avenue
P.O. Box 33510
Kansas City, MO 64120-3510

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated March 26, 2003, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Carbamazepine Extended-release Capsules, 300 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> The concentration of the inactive ingredient, (b)(4) (b)(4), in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral dosage form. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, please provide the following:

> Please provide a revised Form FDA 356h with the correct established name, the correct application type box marked and the correct holder of the approved application.
>
> Please provide either a Financial Certification (Form FDA 3454) or a Disclosure Statement (Form FDA 3455) for your bioequivalence studies.

Please provide either a DMF authorization letter from (b) (4), the drug substance manufacturer, or a letter of authorization to allow (b) (4) to act on their behalf.

Please provide a Debarment Certification and a List of Convictions statement from Nostrum Pharmaceuticals, Inc., the ANDA applicant.

Please provide a letter of authorization for the U.S. Agent with an original signature.

Please provide a field copy certification with an original signature.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Emily Thomas
Project Manager
(301) 827-5862

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-697
cc: DUP/Jacket
HFD-92
Field Copy
HFD-600/Reading File
HFD-610/PRickman
HFD-615/MBennett
Endorsement:
HFD-615/GDavis, Chief, RSB Davis 14-MAY-2003 date
HFD-615/EThomas, CSO Emily Thomas 5/2/03 date
Word Document V:\Firmsnz\nostrum\ltrs&rev\76697.rtf
F/T EST5/6/03
ANDA Refuse to File!

MARTEC
SCIENTIFIC, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

(b) (4)

(b) (4)

ANDA 76-697

May 20, 2003

Mr. Gary Buehler.
Director
Office of Generic Drugs
CDER, FDA
7500 Standish Place
Rockville, MD 20857

ORIG AMENDMENT

Amendment to Original submission for Carbamazepine Extended-release Capsules, 300 mg. ANDA 76-697

Dear Mr. Buehler:

Nostrum Pharmaceutical, Inc, via its agent Paul Sudhakar of Martec scientific, in accordance with 21 CFR 314.99 is filing an amendment to our abbreviated new drug application (ANDA 76-697) dated March 26, 2003, submitted under Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Carbamazepine Extended-release Capsules, 300 mg.

The refusal to file letter is presented as Appendix I and the firms response is provided as Appendix II.

Please contact me at 800-822-6782 or 816-241-4144, of you should need additional information.

Sincerely,

Paul T. Sudhakar
President/CEO
Martec Scientific, Inc.
US Agent for Nostrum Pharmaceutical, Inc.

Encl: Form 356h
Appendix I – Refusal to file letter of May 14, 2003
Appendix II – Firms response

RECEIVED
MAY 2 1 2003
OGD / CDER

ANDA 76-697

Martec Scientific, Inc.
U.S. Agent for Nostrum Pharmaceuticals, Inc.
Attention: Paul T. Sudhakar
1800 N. Topping Avenue
P.O. Box 33510
Kansas City, MO 64120-3510

JUN 23 2003

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the "Refuse to Receive" letter dated May 14, 2003 and your amendment dated May 20, 2003.

Reference is also made to the telephone conversation dated June 16, 2003 and your correspondence dated June 17, 2003.

NAME OF DRUG: Carbamazepine Extended-release Capsules, 300 mg

DATE OF APPLICATION: March 26, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 21, 2003

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice.

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement, or a settlement agreement, or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Thomas Hinchliffe
Project Manager
(301) 827-5849

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-697
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB 23-JUN-2003 date
HFD-615/EThomas, CSO 6/23/03 date
Word File V:\Firmsnz\nostrum\ltrs&rev\76697.ack
FT/EST06/13/03
ANDA Acknowledgment Letter!

MARTEC
SCIENTIFIC, INC.
1800 N. TOPPING
P.O. BOX 33510
KANSAS CITY, MO 64120-3510

PATENT Amendment to ANDA 76-697

August 11, 2003

NEW CORRESP
(NC)
NAI
9/3/03

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – Room 260
7500 Standish Place
Rockville, MD 20855-2773

Re: **PATENT Amendment** to ANDA 76-697 for Carbamazepine Extended-release Capsules, 300 mg.

Dear Mr. Buehler:

In accordance with 21 CFR 314.95(b), Nostrum Pharmaceuticals, Inc., is providing this Patent amendment to provide certification that it has notified the patent and NDA holder identified in its original drug application per 21 CFR 314 .95(a) in accordance with the notice content requirements under 314.95(c). (Presented as **Appendix I**)

In accordance with 21 CFR.95 (e), the notification letter and return receipt acknowledging receipt by the firm is provided in this amendment as **Appendix II.**

A copy of the ANDA acceptance letter is presented as **Appendix III.**

Please contact me at (816) 241-4144 or at 800-822-6782, if additional information is required.

Sincerely,

RECEIVED
AUG 12 2003
OGD/CDER

Paul T. Sudhakar
President/CEO
Martec Scientific, Inc.
Agent for Nostrum Pharmaceuticals, Inc.

Enclosures:

Appendix I: Notification letter and firm's acknowledgement of receipt
Appendix II: OGD ANDA filing acceptance letter

MINOR AMENDMENT

ANDA 76-697

#1

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT - 2 2003

APPLICANT: Martec Scientific, Inc. (U.S. Agent for Nostrum Pharmaceuticals, Inc.)

ATTN: Paul T. Sudhakar

TEL: 816-241-4144

FAX: 816-483-5432

PROJECT MANAGER: 301-827-5849

FROM: Nicole Park

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-release Capsules, 300 mg.

Reference is also made to your amendment(s) dated: May 20, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (5 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Following this page, 4 pages withheld in full - (b)(4)

37. Please acknowledge that results of stability studies should be reported in annual reports in accordance with 21 CFR 314.81. Also, please revise your post-approval stability commitment to include the first three commercial production lots of the product packaged in the smallest and largest container/closure system in the long term stability program. The same applies to the lots placed in stability on a yearly basis.

Sincerely yours,

Brenda J. Uratani /for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

NAI RR + CA '01 + 1576 10/29/03

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

PATENT AMENDMENT

Amendment to ANDA 76-697

October 14, 2003

NEW CORRESP
NC

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – Room 260
7500 Standish Place
Rockville, MD 20855-2773

RE: Patent amendment to ANDA for Carbamazepine Extended-release Capsules, 300 mg. ANDA 76-697

Dear Mr. Buehler:

Nostrum Pharmaceutical, Inc., herewith submits a patent amendment to the above-mentioned ANDA.

In accordance with 21 CFR 314.95(b), Nostrum has notified all the patent and NDA holders identified in our original drug application per the requirements under 314.95(c). The notification letters and return receipts acknowledging receipt by each person are also provided in this amendment as ***Appendix I***. The patent holder Shire Pharmaceuticals has filed a complaint which is presented as ***Appendix II.***

Please contact the agent for Nostrum, Mr. Paul T. Sudhakar at (816) 507-8249 if additional information is required.

Sincerely,

RECEIVED
OCT 15 2003
OGD/CDER

Paul T. Sudhakar
Agent for Nostrum Pharmaceutical, Inc.

Enclosures:

1. **Appendix I:** Notification letters & certified mail receipts and copies of return receipt acknowledging the receipt of the notification.
2. **Appendix II**: Copy of complaint filed by Shire.

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

October 18, 2003

Mr. Gary J. Buehler
Director
Office of Generic Drugs
Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Re: Abbreviated New Drug Application (ANDA 76-697)
Carbamazepine Extended-release capsules, 300 mg

Dear Mr. Buehler:

Please accept this letter as authorization for Paul T. Sudhakar with address at 6739 Vahalla Ct., Shawnee, KS 66217 to act as its agent for Nostrum Pharmaceuticals, Inc. with respect to the aforementioned ANDA submission and regulatory processes. All correspondence related to this ANDA submission and review process should be directed to him.

Addresss: 6739 Vahalla Ct.
Shawnee, KS 66217

Tel: 816-507-8249
Fax: 913-962-9061

Also, please note that we are withdrawing Martec Scientific, Inc,. as its agent effective October 18, 2003.

Should you have any questions or comments, please do not hesitate to contact the undersigned at (732) 355-1411 or Paul Sudhakar at (816) 507-8249

Sincerely,

Nirmal Mulye, Ph.D.
President/CEO

c.c. Paul Sudhakar

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL: NOSTRUMPHARMA@AOL.COM

October 28, 2003

[redacted] CORRESP
NC

Mr. Gary J. Buehler
Director
Office of Generic Drugs
Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NOT
11-17-2003
Dingert

Re: Abbreviated New Drug Application (ANDA 76-697)
Carbamazepine Extended-release capsules, 300 mg

Dear Mr. Buehler:

Please accept this letter as authorization for Paul T. Sudhakar with address at 6739 Vahalla Ct., Shawnee, KS 66217 to act as its agent for Nostrum Pharmaceuticals, Inc. with respect to the aforementioned ANDA submission and regulatory processes. All correspondence related to this ANDA submission and review process should be directed to him.

Addresss: 6739 Vahalla Ct.
Shawnee, KS 66217

Tel: 816-507-8249
Fax: 913-962-9061

Should you have any questions or comments, please do not hesitate to contact the undersigned at (732) 355-1411 or Paul Sudhakar at (816) 507-8249.

Sincerely,

Nirmal Mulye, Ph.D.
President/CEO

c.c. Paul Sudhakar

RECEIVED
NOV 0 5 2003
OGD/CDER

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

MINOR Amendment ANDA 76-697

December 12, 2003

ORIG AMENDMENT
N/AM

Mr. Gary Buehler.
Director
Office of Generic Drugs
CDER, FDA
Rockville, MD 20857

RE: MINOR Amendment to ANDA 76-697 for Carbamazepine Extended-release Capsules, 300 mg.

Dear Mr. Buehler:

Nostrum, Inc., via its agent Paul Sudhakar, is filing chemistry and manufacturing amendment in accordance with 21 CFR 314.99 and your deficiency letter of October 2, 2003, for its abbreviated new drug application (ANDA) for Carbamazepine Extended-release Capsules, 300 mg (ANDA 76-697).

The deficiency letter is presented as Appendix I, and the firm's response in the same order as it appears in the deficiency letter is provided as Appendix II.

Please contact me at 816-507-8249 if you should need additional information.

Sincerely,

Paul T. Sudhakar.
Agent for Nostrum Pharmaceuticals, Inc.

Enclosures:

Appendix I: Deficiency letter of October 2, 2003
Appendix II: Firm's response as Minor Amendment

RECEIVED
DEC 15 2003
OGD/CDER

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

LABELING Amendment to ANDA 76-697

January 19, 2004.

ORIG AMENDMENT
N/AF

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – Room 260
7500 Standish Place
Rockville, MD 20855-2773

Re: **Labeling Amendment** to ANDA **76-697** for Carbamazepine Extended-release Capsules, 300 mg

Dear Mr. Buehler:

Nostrum Pharmaceuticals, Inc., herewith submits a **labeling** Amendment in accordance with 21 CFR 314.96 and the labeling deficiency letter to to ANDA **76-697** Carbamazepine Extended-release Capsules, 300 mg.

The labeling deficiency letter is provided as **Appendix I** and the response to this letter is provided as **Appendix II**. Two copies are provided one for Archival purpose and one for Review purpose. Electronic versions of the labeling and side-by-side comparisons is also provided in the enclosed CD.

Please contact me at (816) 507-8249 or by fax at 013-062-9061 if additional information is required.

Sincerely,

Paul T. Sudhakar
Agent for Nostrum Pharmaceuticals, Inc.

RECEIVED
JAN 2 0 2004
OGD/CDER

BIOEQUIVALENCY AMENDMENT

ANDA 76-697

FEB 03

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Nostrum Pharmaceuticals, Inc.; c/o Martec Pharmaceuticals, Inc.

TEL: 816-241-4144

FAX: 816-483-5432

ATTN: Paul Sudhakar

PROJECT MANAGER: 301-827-5847

FROM: Steven Mazzella

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 26, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-Release Capsules, 300 mg.

Reference is also made to your amendment(s) dated: .

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

FEB 03 2004

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-697 APPLICANT: Nostrum Pharmaceuticals, Inc

DRUG PRODUCT: Carbamazepine ER Capsules, 300 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. Please submit a bioequivalence study in which the test and reference products are administered by sprinkling the capsule contents over a spoonful of applesauce. Subjects should be fasted overnight before receiving the study drugs in applesauce. The sprinkle study is requested to support the relevant labeling of this product. Bioequivalence assessment will be based on carbamazepine data.

2. Please conduct comparative dissolution testing of the test and reference products using:

   a) USP Apparatus I (Basket) at 100 rpm in 900 ml water, pH 1.2, 4.5 and 6.8 with and without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs.

   b) USP Apparatus II (Paddle) at 50 rpm and 75 rpm in 900 ml water, pH 1.2, 4.5 and 6.8 with and without 0.1% SLS. Sampling times: 1,2,4,6,8,10 and 12 hrs.

   c) In addition, please use the following dissolution method:

      USP Apparatus II (Paddle) at 75 RPM
      Medium: 900 ml of dissolution media
      First 4 hrs: pH 1.1 HCl
      After 4 hrs: pH 7.5 phosphate buffer with 0.1% SLS
      Sampling times: 1, 4, 6 and 12 hrs

The use of higher SLS concentration should be justified and fully documented.

Sincerely yours,

for Barbara M Davit

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL.: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

LABELING Amendment to ANDA 76-697

ORIG AMENDMENT

February 23, 2004.

N/AF

FPL

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – Room 260
7500 Standish Place
Rockville, MD 20855-2773

Re: **Labeling Amendment** to ANDA **76-697** for Carbamazepine Extended-release Capsules, 300 mg

Dear Mr. Buehler:

Nostrum Pharmaceuticals, Inc., herewith submits a **labeling** Amendment in accordance with 21 CFR 314.96 and the labeling deficiency letter to ANDA **76-697** Carbamazepine Extended-release Capsules, 300 mg.

The labeling deficiency letter is provided as **Appendix I** and the response to this letter is provided as **Appendix II**. Two copies are provided one for Archival purpose and one for Review purpose. Electronic versions of the labeling and side-by-side comparisons is also provided in the CD enclosed in the Archival copy.

Please contact me at (816) 507-8249 or by fax at 913-962-9061 if additional information is required.

Sincerely,

Paul T. Sudhakar
Agent for Nostrum Pharmaceuticals, Inc.

RECEIVED
FEB 24 2004
OGD/DDR

MINOR AMENDMENT

#7

ANDA 76-697

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAR 17 2004

APPLICANT: Nostrum Pharmaceuticals, Inc.

TEL: 732-355-1411

ATTN: Paul T. Sudhakar

FAX: 732-355-1271

FROM: Nicole Lee

PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamezepine Extended-release Capsules USP, 300 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

M

Following this page, 2 pages withheld in full - (b)(4)

RECORD OF TELEPHONE CONVERSATION

I telephoned Mr. Sudhakar and requested the following change pre approval;

INSERT
DOSAGE AND ADMINISTRATION, Epilepsy, third sentence; change "1200 daily" to "1200 mg daily"

Mr. Sudhakar will submit a commitment to make the above change.

DATE

March 22, 2004

ANDA NUMBER

76-697

IND NUMBER

TELECON

INITIATED BY APPLICANT/ SPONSOR X **FDA**

MADE BY TELE. X **IN PERSON**

PRODUCT NAME

Carbamazepine Extended-Release Capsules

FIRM NAME

Nostrum Pharmaceuticals, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Paul T. Sudhakar

TELEPHONE NUMBER

816-507-8249

SIGNATURE

V:\FIRMSNZ\NOSTRUM\TELECONS\76697.tcon032204.DOC

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

Bioequivalency Amendment to ANDA **76-697**

October 5, 2004

ORIG AMENDMENT

N|AB

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – Room 260
7500 Standish Place
Rockville, MD 20855-2773

Re: **Bioequivalency Amendment** to ANDA 76-697 for Carbamazepine ER 300 mg Capsules

Dear Mr. Buehler:

In accordance with 21 CFR 314.96 and the bioequivalency deficiency letter of February 03, 2004 Nostrum Pharmaceuticals, Inc., (presented as Appendix I) herewith submits a bioequivalency Amendment for Carbamazepine ER 300 mg Capsules ANDA 76-697.

The amendment contains a full bioequivalency study of Carbamazepine 300 mg ER Sprinkle Study – Nostrum B044401 and all the dissolution test data and results required per the deficiency letter of February 03, 2004. The SAS transport raw data diskette is presented in the Archival copy only.

The amendment consists of 4 volumes of the Archival copy and 4 volumes of the Review copy for a total of 8 volumes in this shipment.

Please contact me at (816) 507-8249 or at 913-233-0054 ext 101 if additional information is required.

Sincerely,

Paul T. Sudhakar
Agent for Nostrum Pharmaceuticals, Inc.

Enclosures: **Data Diskette (immediately after the cover letter)**
FDA 356h form
Appendix I: Deficiency letter of February 03, 2004.
Appendix II: Firm's response

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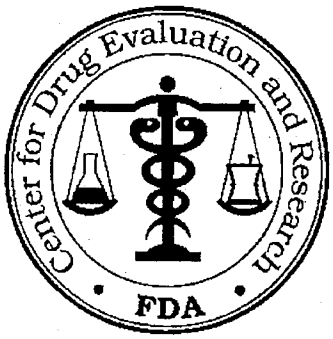
OCT 12 2004
OGD/CDER

BIOEQUIVALENCY AMENDMENT

ANDA 76-697

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

NOV 19 2004



APPLICANT: Nostrum Pharmaceuticals, Inc.; c/o Martec Pharmaceuticals, Inc.

TEL: 816-507-8247

FAX: 913-962-9061

ATTN: Paul Sudhakar

PROJECT MANAGER: 301-827-5847

FROM: Steven Mazzella

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on October 5, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-Release Capsules, 300 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

AB

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-697 APPLICANT: Nostrum Pharmaceuticals, Inc

DRUG PRODUCT: Carbamazepine ER Capsules, 300 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Your proposed dissolution method and specifications are not acceptable. Your dissolution data are acceptable. However, please acknowledge that you have accepted the following dissolution method and specifications:

The dissolution testing should be conducted in 900 mL of pH 1.2 buffer with 0.1% SLS using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following FDA recommended specifications:

1 hr	(b) (4) %
4 hr	%
8 hr	%
12hr	NLT (b) (4) %

Sincerely yours,

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

MINOR Amendment ANDA 76-697

December 30, 2004

Mr. Gary Buehler.
Director
Office of Generic Drugs
CDER, FDA
Rockville, MD 20857

ORIG AMENDMENT

N/Am

RE: MINOR Amendment to ANDA 76-697 for Carbamazepine Extended-release Capsules, 300 mg.

Dear Mr. Buehler: 3/17/04

Nostrum, Inc, via its agent Paul Sudhakar, is filing chemistry and manufacturing amendment in accordance with 21 CFR 314.99 and your deficiency letter of March 17, 2003, to its abbreviated new drug application (ANDA) for Carbamazepine Extended-release Capsules, 300 mg. (ANDA 76-697)

The deficiency letter is presented as Appendix I and the firms response in the same order as it appears in the deficiency letter is provided as Appendix II.

Please contact me at 816-507-8249 if you should need additional information.

Sincerely,

Paul T. Sudhakar.
Agent for Nostrum Pharmaceutical, Inc.

Enclosures:

Appendix I: Deficiency letter of March 17, 2004
Appendix II: Firms response as Minor Amendment

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NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

Bioequivalency Amendment to ANDA **76-697**

December 30, 2004

ORIG AMENDMENT

N/AB

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
MPN II, HFD 600 – Room 260
7500 Standish Place
Rockville, MD 20855-2773

Re: **Bioequivalence Amendment** to ANDA 76-697 for Carbamazepine ER 300 mg Capsules

Dear Mr. Buehler:

In accordance with 21 CFR 314.96 and the bioequivalency deficiency letter of November 19, 2004, Nostrum Pharmaceuticals, Inc., (presented as Appendix I) herewith submits a bioequivalence Amendment for Carbamazepine ER 300 mg Capsules ANDA 76-697.

Please contact me at (816) 507-8249 or at 913-233-0054 ext 101 if additional information is required.

Sincerely,

Paul T. Sudhakar
Agent for Nostrum Pharmaceuticals, Inc.

Enclosures: **FDA 356h form**
Appendix I: Deficiency letter of November 19, 2004.
Appendix II: Firm's response

RECEIVED
JAN 0 3 2005
OGD / CDER

Archival Copy

ORIG AMENDMENT

N/AM

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

Telephone Amendment ANDA 76-697

April 24, 2005

Mr. Gary Buehler.
Director
Office of Generic Drugs
CDER, FDA
Rockville, MD 20857

RE: Telephone Amendment to ANDA 76-697 for Carbamazepine Extended-release Capsules, 300 mg.

Dear Mr. Buehler:

In accordance with 21 CFR 314.99 and a telephone communication from Ms. Damaris Maldonado on April 6, 2005, Nostrum, Inc, via its agent Paul Sudhakar, is filing a telephone amendment to its abbreviated new drug application (ANDA) for Carbamazepine Extended-release Capsules, 300 mg. (ANDA 76-697).

The reviewers request and the firms response is presented as Appendix I. A courtesy copy has been sent to Ms. Maldonado by facsimile. Enclosed herewith are the archival and review copies.

Please contact me at 816-507-8249 if you should need additional information.

Sincerely,

Paul T. Sudhakar.
Agent for Nostrum Pharmaceuticals, Inc.

Enclosures:

Appendix I: Reviewers request of April 6, 2005 and Firms response
Attachment 1: Dissolution test data

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APR 26 2005
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ARCHIVAL COPY

MAJOR AMENDMENT

ANDA 76-697

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 27 2005

APPLICANT: Nostrum Pharmaceuticals, Inc. TEL: 816-507-8249

ATTN: Paul Sudhakar FAX: 913-962-9061

FROM: Yoon Kong PROJECT MANAGER: (301) 827-5791

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-release Capsules, 300 mg.

Reference is also made to your amendment dated December 30, 2004; and April 24, 2005.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

UK 6/24/05

Following this page, 1 page withheld in full - (b)(4)

3. The Division of Bioequivalence is being informed of these manufacturing concerns. Please contact the Division for any additional bioequivalence requirements.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

Amendment ANDA 76-697

November 22, 2005

ORIG AMENDMENT

N/AC

Mr. Gary Buehler.
Director
Office of Generic Drugs
CDER, FDA, MPN II
7500 Standish Place
Rockville, MD 20857

RE: Amendment to ANDA 76-697 for Carbamazepine Extended-release Capsules, 300 mg.

Dear Mr. Buehler:

Nostrum Pharmaceuticals, Inc, via its agent Paul Sudhakar, is filing chemistry and manufacturing amendment in accordance with 21 CFR 314.96 and your deficiency letter of June 27, 2005, to its abbreviated new drug application (ANDA) for Carbamazepine Extended-release Capsules, 300 mg (ANDA 76-697)- (Deficiency Letter is provided as Appendix I). Detailed response to each of your comments in the Major deficiency letter is provided in this amendment as Appendix II.

This ANDA was under review for more than two years before the agency issued the June 27, 2005 deficiency letter. During that period, the agency conducted at least two CMC reviews and issued two Minor CMC Deficiency Letters (October 2, 2003 and March 17, 2004). At no time during that extended review process did the Agency indicate that the Nostrum process (b) (4) to the extent that commercial scale-up batch manufacturing would be considered unreliable or unacceptable. We find it difficult to comprehend how we could receive a MAJOR deficiency notification now -- 27 months after the submission of the application -- when the earlier reviews generated only MINOR deficiency notices to which we fully and completely responded. As we are sure you can understand, this delayed action by the agency has placed a serious burden on the firm and poses the potential for significant economic loss. We urge you to reconsider this action in light of the enclosed detailed submissions, and revise the current deficiencies to Minor Amendment.

The CMC deficiency letter of June 27, 2005 required that we contact the Division of Bioequivalence, therefore we are providing two copies of this amendment to the Division of Bioequivalence for archival and review purposes under a separate cover.

We believe that a meeting to discuss the deficiency notice and our response would be

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NOV 23 2005
OGD / CDER

useful, and are ready and willing to meet with you to discuss this matter as soon as possible.

Please contact me at 816-507-8249 if you should need additional information.

Sincerely,

Paul T. Sudhakar.
Agent for Nostrum Pharmaceuticals, Inc.

Enclosures:

Appendix I: Deficiency letter of June 27, 2005
Appendix II: Firms response with request to reclassify as Minor Amendment

NOSTRUM PHARMACEUTICALS, INC.

203 SOMERSET CT. PRINCETON, NJ 08540 · TEL: (732) 355 1411 · FAX: (732) 355 1271 EMAIL : NOSTRUMPHARMA@AOL.COM

Amendment ANDA 76-697

November 22, 2005

Mr. Gary Buehler.
Director
Office of Generic Drugs
CDER, FDA, MPN II
7500 Standish Place
Rockville, MD 20857

RE: CMC Amendment to ANDA 76-697 for Carbamazepine Extended-release Capsules, 300 mg. Copies for Bioequivalence of Division

Dear Mr. Buehler:

Nostrum, Pharmaceuticals, Inc, via its agent Paul Sudhakar, is herewith providing two copies to Division of Bioequivalence of the chemistry and manufacturing amendment filed on November 22, 2005. This amendment to its abbreviated new drug application (ANDA) for Carbamazepine Extended-release Capsules, 300 mg (ANDA 76-697) has been filed in accordance with 21 CFR 314.96 and the CMC deficiency letter of June 27, 2005,. Response to each of the CMC comments in the Major deficiency letter is provided in this amendment as Appendix II.

The CMC deficiency letter of June 27,2005 required that we contact the Division of bioequivalence. (**FDA COMMENT 3:** The Division of Bioequivalence is being informed of these manufacturing concerns. Please contact the Division for any additional bioequivalence requirements.). Therefore we are providing these two copies of the entire amendment for your information. The two copies are for archival and review purposes.

Please contact me at 816-507-8249 if you should need additional information.

Sincerely,

Paul T. Sudhakar.
Agent for Nostrum Pharmaceuticals,Inc.

Enclosure:

Entire CMC Amendment of November 22, 2005. – Two Copies

March 09, 2006

From: Nostrum Pharmaceuticals, Inc,
505 Thornall Street, #304
Edison, New Jersey 08837

Correspondence to ANDA 76-697

MC

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA, MPN II
7500 Standish Place
Rockville, MD 20857

RE: Correspondence to ANDA 76-697 for Carbamazepine Extended-release Capsules, 300 mg.

Dear Mr. Buehler:

Nostrum Pharmaceuticals, Inc, via its agent Paul Sudhakar, herewith is filing the attached new correspondence to the chemistry and manufacturing section of its abbreviated new drug application (ANDA) for Carbamazepine Extended-release Capsules, 300 mg (ANDA 76-697).

Please contact me at 816-507-8249 if you should need additional information.

Sincerely,

Paul T. Sudhakar

Paul T. Sudhakar
Agent for Nostrum Pharmaceuticals, Inc.

MAJOR AMENDMENT

#4

ANDA 76-697

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAY 01 2006

APPLICANT: Nostrum Pharmaceuticals, Inc.

TEL: 816-507-8247 or 913-233-0054 ext.101

ATTN: Paul T. Sudhakar

FAX: 913-962-9061

FROM: Yoon Kong

PROJECT MANAGER: (301) 827-5791

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-release Capsules, 300 mg.

Reference is also made to your amendment dated November 22, 2005.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachment (__1__ page). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

YL 4/25/06

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-697 APPLICANT: Nostrum Pharmaceuticals, Inc.

DRUG PRODUCT: Carbamazepine Extended-release Capsules USP, 300 mg

The deficiencies presented below represent MAJOR deficiencies.

We raised several questions relative to [redacted] (b) (4) batch records in our June 27, 2005, Major Deficiency letter. We further emphasize these comments as follows:

> The Office of Generic Drugs uses data generated on the ANDA pivotal batch not only to demonstrate bioequivalence to the Reference Listed Drug, but also as a quality benchmark. Because of the importance of this batch, it is essential that details of its manufacture be unassailable. Since the manufacture of your exhibit batch, you have agreed to the addition of several critical drug product manufacturing process controls, including control of [redacted] (b) (4)
>
> Therefore, please manufacture a new test batch and contact our Division of Bioequivalence for *in vivo* bioequivalence study requirements. Please also be advised that the adequacy of your manufacturing process controls will be further evaluated upon review of the new exhibit batch. Finally, it is also recommended that the root cause(s) of the [redacted] (b) (4) problem be determined as well as identification of appropriate corrective measures in your next amendment.

Sincerely yours,

M. Scott Furumoto for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

NOSTRUM PHARMACEUTICALS, INC.

505 THORNALL STREET, EDISON, NJ08837 · TEL: (732) 635 0036 · FAX: (732) 635 0042 EMAIL : NIRMAL@NOSTRUMPHARMA.COM

May 17, 2006

Gary J. Buehler
Director, Office of Generic Drugs,
CDER, FDA, HFD-600
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD, 20855-2773
(301-594-0320)

Re: ANDA-76-697, Carbamazepine Extended-Release Capsule, USP, 300 mg
Via Certified Mail, Fax : 301-443-3839, 240-276-9327

Dear Mr. Buehler, ATTN: FLORENCE FANG

Please be advised that Nostrum Pharmaceuticals, the sponsor of this ANDA, wishes to modify the registered agent for this ANDA. As of this date, the registered agent and the principal contact for the FDA concerning this ANDA is:

cGxP Consulting
Hugh Grimes
25 Harbor Drive, Suite 101
Vernon Hills, IL, 60061
Ph: (847)- 549- 0626, 111
Fax: (847)- 549- 0626
hggrimes@cgxp.com

All communication about this ANDA must go through Hugh Grimes and cGxP Consulting.

Please delete Paul Sudhakar, Ph.D. as the registered agent for this ANDA and do not communicate with him further.

Thank you in advance for your consideration.

Sincerely,

Nirmal Mulye, Ph.D.
President

Gary J. Buehler
Director, Office of Generic Drugs,
CDER, FDA, HFD-600
Document Control Room, Metro
Park North II
7500 Standish Place, Room 150
Rockville, MD, 20855-2773
(301-594-0320)

cGxP
Hugh Grimes
25 Harbor Drive, Suite 101
Vernon Hills, IL, 60061
Ph: (847)- 549- 0626, 111
Fax: (847)- 549- 0626
hggrimes@cgxp.com

5/16/06

Via Certified Mail, Fax : 301-443-3839, 240-276-9327

Re: ANDA-76-697,
Carbamazepine Extended-Release Capsule, USP, 300 mg

Dear Mr. Buehler,

We have been retained by (b) (4) (b) (4), an interested party in the above referenced ANDA, along with the registered ANDA holder, Nostrum Pharmaceuticals, Inc. ("Nostrum").

We have received your Fax dated 5/1/06 (copy attached) in regards to Nostrum's application for Carbamazepine, in which you raised several questions relative to the (b) (4) in the exhibit batch records discussed in your June 27, 2005 Major Deficiency Letter. We agree that the next batch produced is quite important and that the details of its manufacture be unassailable.

Towards that end, we would like to request a meeting with you and your Bioequivalence and CMC staff in Rockville, at your earliest convenience. Aside from discussions we would like to have with you on regulatory/ scientific/ technical aspects, there are a number of personnel changes we would like to introduce your groups to surrounding this ANDA.

We propose an agenda below. The attendees from our side have been asterisked in the cc.

1. Introduction and Management Mission of (b) (4) (b) (4)
2. Introduction and Mission of Hugh G. Grimes, the President/CEO of cGxP who will become the new registered agent for this ANDA.
3. How we intend to handle the transition of the registered agent to cGxP from Paul Sudhakar. (Nostrum Pharmaceuticals).
4. How we have identified the root causes responsible for the issues with the original "filing batch."
5. How we currently propose corrective actions that will make the process robust and reproducible, and achieve greater (b) (4).

cc: Florence Fang, (FDA, HFD-640 Division of Chemistry II) Fax: 301- 443-3839,
Yoon Kong, (FDA, Project Manager Team 7, HFD- 640) Fax: 301-594-0320,
Dale Conner Pharm. D., (Deputy Director, FDA HFD-651, Div of Bioequivalenece, Fax 301-594-0180),
(b) (4)
Paul T Sudhakar, Ph.D.* (Nostrum Pharmaceuticals),
and (b) (6) * (cGxP)

A8.1

ORIG AMENDMENT

N-000-MC

Mr. Gary J. Buehler
Director, Office of Generic Drugs,
CDER, FDA, HFD-600
Document Control Room,
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD, 20855-2773
(301-594-0320)

cGxP
Hugh Grimes
25 Harbor Drive, Suite 101
Vernon Hills, IL, 60061
Ph: (847)- 549- 0626, 111
Fax: (847)- 549- 0626
hggrimes@cgxp.com

Via Certified Mail, Fax : 301-443-3839, 240-276-9327

Re: Intent to Amend ANDA-76-697,
Carbamazepine Extended-Release Capsule, USP, 300 mg

Dear Mr. Buehler,

We sent two letters to your office 5/19/06. One Letter came from Nostrum Pharmaceuticals, the sponsor of the ANDA, and authorized cGxP to be the new registered agent for this ANDA. The other letter was from cGxP and requested an opportunity to meet with your office. We were responding to the Not Approvable Deficiency Letter 5/1/06. We are in the process of collecting information and discussing this opportunity with your staff.

Amidst all the changes, we overlooked 21 CFR §314.120 (1). Hence, this letter constitutes notice of our intent to file a Major Amendment in response to that Not Approvable Letter. As per 21 CFR § 314.60 and §314.96, we intend to file a major amendment containing significant data or information to resolve deficiencies in the application as set forth in the deficiency letter.

Please feel free to contact me at any time, if you have any questions.

Sincerely,

Hugh Grimes, President cGxP

6/2/06

Serving Drug, Device, and Biotech Industries in Quality Systems and Regulatory.

cc: (b) (4)

NOSTRUM
Pharmaceuticals, Inc.

505 Thornall Street, Suite 304, Edison NJ 08837 Tel: 732-635-0036 Fax: 732-635-0042

February 8, 2007

Mr. Gary J. Buehler R. Ph.
Director, Office of Generic Drugs,
CDER, FDA, HFD-600
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MC

Re: ANDA -76-697, Carbamazepine Extended-Release Capsule, USP, 300mg

Dear Mr. Buehler,

Please be advised that Nostrum Pharmaceuticals, Inc. the sponsor of this ANDA, wishes to modify the registered agent for this ANDA. As of this date, the registered agent and the principal contact for the FDA concerning this ANDA is:

Dr. Dhiren Shah
Nostrum Laboratories, Inc
1800 N. Topping Ave.
Kansas City, MO 64120
(816) 308-4970
Email: dshah@nostrumlabs.com

All communication about this ANDA must go through Dr. Dhiren Shah of Nostrum Laboratories, Inc.

Please delete Hugh Grimes as the registered agent for this ANDA and do not communicate with him further.

Thank you in advance for your consideration.

Sincerely,

Nirmal Mulye, Ph.D.
President

cc: Dr. Dhiren Shah, NLI, Kansas City, MO

NOSTRUM
LABORATORIES, INC.

1800 N Topping Ave, Kansas City, MO 64120 Tel: 816 841 4636 Fax: 816 841 4634

March 30, 2007

Office of Generic Drugs
Food and Drug Administration
Metro Park North 4 (MPN 4), HFD-600
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N. AC

Attention: Mr. Gary J. Buehler, Director

Re: ANDA # 76-697
Carbamazepine Extended-Release Capsules, USP, 300mg

Amendment:
Chemistry, Manufacturing, and Controls
Response to FDA Fax Letter Dated
May 01, 2006

Dear Mr. Buehler:

Please refer to the agency's fax letter, dated May 01, 2006, (Exhibit 1) to the above-referenced Abbreviated New Drug Application # 76-697 for Carbamazepine Extended-Release Capsules, USP, 300 mg. The agency letter provided Chemistry comments on the application.

The purpose of this amendment to the application, in triplicate, is to provide a complete response to the agency's comments. The first and second copies are Archival and Review. The third copy of this submission is for the Division of Bioequivalence. This submission contains one volume.

The enclosed document (Exhibit 2) provides detailed responses to the agency's comments and supporting technical information and data. The salient points of this submission are:

- Nostrum has provided a detailed Amendment Overall Summary (AOS) containing:
  - Scientific discussion on the drug product manufacturing process
  - Drug product understanding
  - Drug product manufacturing process understanding
  - Comparison between the original Bio-Batch and the new Test/Exhibit Batch
  - Root cause analysis of the [redacted] (b) (4) problem with corrective and preventive measures

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- Nostrum has successfully made a new Test/Exhibit Batch per the agency's instructions. It includes the addition of several critical drug product manufacturing process controls, including control of (b) (4)
  - Blank and Executed Batch Production Records for drug product manufacturing have been included. For review convenience, we indicated the addition of critical process controls by placing "posted notes" on the Batch Production Record with a more detailed explanation on the following page within the Batch Record.
  - Data are provided to show the bead (b) (4) and quality.
  - Please note that with the addition of critical process controls in the drug product manufacturing, the critical process parameters remained constant and unchanged from the original Bio-Batch.
- Data showing chemistry equivalency between the original Bio-Batch and the new Test/Exhibit Batch.
- (b) (4) requirements.

Based on the above discussion and enclosed data, Nostrum concludes that the original Bio-Batch is equivalent to the new Test/Exhibit Batch. The original Bio-Batch meets the criteria for strength, identity, purity, potency, and quality. It also provides assurance to the agency that any future batches of this product will strictly meet the (b) (4) requirement of the USP and the agency.

Nostrum's additional commitment to the Agency:

For a period of time as assessed by the agency, Nostrum commits to submit the capsule (b) (4) data and the product assay data on each and every batch of the drug product produced for commerce and secure the agency's approval on each batch prior to commercialization. This commitment assures the agency that each and every batch made for commerce will meet the (b) (4) and assay requirements.

Nostrum requests the agency's approval of the application based on this amendment and previous submissions.

Pursuant to 21 CFR 314.50(d)(v), 21 CFR 314.71(b) and 21 CFR 314.97, Nostrum hereby provides an exact copy of this submission to the FDA Kansas City District Office. The undersigned Agent of Nostrum Pharmaceuticals certifies that the Field Copy is an exact copy of this submission.

Should you have any questions or comments on this submission, please feel free to contact the undersigned at (816) 308-4970, by fax at (816) 841-4634, or by e-mail at dshah@nostrumlabs.com.

Sincerely,

Dhiren N. Shah

Dhiren N. Shah, Ph.D., RAC
(Agent for Nostrum Pharmaceuticals, Inc.)
President/COO and Head of Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120

Enclosure

cc: Dr. Scott Furness, Team Leader and Senior Regulatory Review Chemist, OGD (Desk Copy)
Dr. Thomas Hinchliffe, Project Manager, OGD (Desk Copy)
Dr. Chandra Chaurasia, Team Leader, DOB (Desk Copy)
Ms. Shirley J. Berryman, New Product Pre-Approval Manager, KC District Office, FDA (Field Copy)

NOSTRUM
LABORATORIES, INC.

1800 N Topping Ave, Kansas City, MO 64120 Tel: 816 841 4636 Fax: 816 841 4634

August 22, 2007

Office of Generic Drugs
Food and Drug Administration
Metro Park North 4 (MPN4), HFD-600
7519 Standish Place
Rockville, MD 20855

MC

Attention: Ms. Theresa Liu, Project Manager, Div of Chemistry-II

Re: ANDA # 76-697 **Meeting Request**
Carbamazepine Extended-Release Capsules, 300mg

Dear Ms. Liu:

This is to follow up on our telephone discussion of August 16, 2007. By letter dated August 13, 2007, the CMC Division asked Nostrum for a "new bioequivalence study" and requested that Nostrum "contact the Division of Bioequivalence for the appropriate *in vivo* bioequivalence study requirements."

Nostrum would like a face to face meeting with the Agency to discuss its above-referenced ANDA for Carbamazepine Extended Release Capsules, 300 mg. More particularly, the purpose of this meeting request is to (i) discuss the CMC Division's request for a new bioequivalence study, notwithstanding that the original studies demonstrated bioequivalence to the satisfaction of the Division of Bioequivalence, and (ii) present new data from Nostrum's investigation of the process, from which Nostrum concludes that the (b) (4) and quality is not in question and is not the root cause of the small incidence of (b) (4) that were discovered in Lot # 20313. Nostrum respectfully requests the presence of Mr. Gary Buehler, and CMC and Bioequivalence staff members of the OGD: Ms. Florence Fang, Dr. Scott Furness, Dr. Damaris Maldonado, Dr. Chandra Chaurasia, and Dr. Barbara Davit at the meeting.

Should you have any question or comments on this communication, please contact the undersigned at (b) (6).

Thank you and best regards.

Suzanne Ahe — for Dhiren Shah

Dhiren N. Shah, Ph.D., RAC
Regulatory Affairs Consultant
Nostrum Laboratories, Inc.
1800 N. Topping Avenue
Kansas City, MO 64120-1228
Tel: (816) 308-4970
Fax: (816) 841-4634
Cell: (b) (6)
e-mail: dshah@nostrumlabs.com

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April 28, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room (HFD-600)
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N AC

Attention: Mr. Gary Buehler, Director, Office of Generic Drugs

Re: ANDA # 76-697
Carbamazepine Extended-Release Capsules

Major Amendment:
CMC & Bioequivalence

Dear Mr. Buehler:

Please refer to the Agency's letter dated August 13, 2007 addressed to Nostrum Pharmaceuticals, (Exhibit # 1) and the teleconference on August 16, 2007 between the Agency and the undersigned about the Abbreviated New Drug Application (# 76-697) for Carbamazepine Extended-Release Capsules.

Brief Background:

The Agency's letter advised Nostrum Pharmaceuticals to conduct a Bioequivalence Study on the drug product manufactured after the inclusion of in-process controls reported in the March 30, 2007 submission.

In the teleconference of August 16, 2007 the following critical points were discussed:

1. Nostrum was pleased to note that the Agency had no negative comments on the March 30, 2007 Amendment (a copy of which is included in this submission for review convenience as Exhibit # 2).
2. The Agency advised Nostrum that it had only given a cursory review of the March 30, 2007 amendment and it will employ its CMC review resources for detailed review of the submission only if the re-made biobatch is found to be bioequivalent to RLD. Nostrum concurred with the agency's reasoning and logic.
3. The agency advised Nostrum to conduct Fasted, Fed, and Sprinkle bioequivalence studies.

4. Nostrum informed the agency that it has developed dose-proportional 100 mg and 200 mg strength capsules and it intends to amend the ANDA with a request for bio-waiver for these two lower strengths. The agency advised Nostrum that if the lower strengths met the requirements of 21 CFR 320.22 then it may submit the bio-waiver request in the ANDA amendment.

Nostrum is pleased to inform the agency that it has completed all three bioequivalence studies per agency's instructions and all three studies meet the FDA requirements for bioequivalence. The result from these studies further supports the data and derived conclusion provided in the March 30, 2007 submission which supports the robustness of the CMC for the drug product.

Purpose of the Submission:

The purpose of this major amendment to the ANDA is to provide CMC, bioequivalence, and labeling information. Nostrum requests the approval of the Abbreviated New Drug Application. This submission, in quadruplet, contains 21 volumes. The first two copies are for archival and review. The third copy of this submission is for the DOB review. The fourth copy of the submission (only labeling section) is for labeling review.

Summary of the Submission:

The enclosure to this letter provides detailed technical CMC information and data; fasted, fed, and sprinkle bioequivalence study reports, and labeling information. The salient points of this submission are:

1. **General**:

   - For review convenience, Nostrum has provided a regulatory chronology of the ANDA since it was submitted.
   - A detailed table of contents has been provided to facilitate easy navigation within the submission.

2. **CMC Information and Data**:

   - Changes in administrative and technical information on the drug substance.
     - (b) (4)
     -
     -

manufacturing or drug product performance, as a result of the change in the (b) (4) process.

- (b) (4)

- Drug product manufacturing which incorporates changes and enhancements as outlined in the March 30, 2007 submission.
  - Incorporation of various in-process controls in the manufacturing of the drug product as previously reported to the Agency in the March 30, 2007 submission.
  - (b) (4)
  - The resultant drug product remains the same as the original biobatch with consistent quality testing results.

- Updated stability data on the 300 mg strength capsules.
  - The three month stability data at accelerated and long-term room temperature conditions show excellent stability of the 300 mg strength capsules
  - Comparison of stability from the original biobatch with this repeat test batch shows excellent equivalence.

- Manufacturing, controls, and the stability of the 100 and 200 mg strength capsules.
  - The same (b) (4) employed for filling the 300 mg strength capsules (size 0 capsules) are employed to fill the 100 mg (size 2 capsules) and 200 mg (size 1 capsules) strength capsules with no change in the manufacturing process or in-process controls, and with specifications based on the 300 mg strength capsules.
  - The three months stability data on both 100 and 200 mg capsules at accelerated and long term room temperature show excellent stability profile and similar to that of the 300 mg capsules.

3. **Bioequivalence and Capsule Dissolution Information and Data**:

- The fasted, fed, and sprinkle bioequivalence study results between the 300 mg strength capsules and the Reference Listed Drug (RLD) (Carbatrol® capsules).
  - The 300 mg strength capsules test product meets the FDA bioequivalence requirements of confidence interval limits for Cmax and AUC equivalence with the RLD product based on each of the three bioequivalence studies.
- The results of the repeat bioequivalence studies are almost identical to the original bioequivalence studies in all aspects, indicating that the drug product manufacturing and the CMC have remained consistent.
- The dissolution profile of the 100 mg, 200 mg, and the 300 mg strength capsules are provided and found to be similar.
- The dissolution release profile comparison between the RLD 300mg and Nostrum product 300 mg strength using 0.1% SLS (FDA recommended) as the dissolution medium are provided.
- Pursuant to 21 CFR 320.22, Nostrum is requesting a bio-waiver for the 100 and 200 mg strength capsules.
- Compact Discs* of the Bioequivalence section is included in the submission.

4. **Labeling**

- Container-closure labels for all three strengths in package counts of 30 and 120 capsules.
- Side-by-side comparison of prescribing information with Reference Listed Drug (Carbatrol®).
- Compact Discs* of labeling and prescribing information in SPL format.

* CD's were scanned with Symantec AntiVirus software.

Based on the enclosed detailed information for all three strengths of capsules and the above analysis, Nostrum concludes that its Carbamazepine Extended-Release Capsules are (i) manufactured using a well-characterized process, (ii) stable, and (iii) bioequivalent. Most importantly, the finished product has remained unchanged since the original ANDA submission with documented improvements and enhancements. The inclusion of in-process controls has resulted in more predictable and (b) (4) drug product manufacturing.

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Nostrum requests the Agency to review this submission and approve the Abbreviated New Drug Application for Carbamazepine Extended-Release Capsules based on the enclosed excellent Bioequivalence Studies results and corresponding CMC information and data. The approval of the submission will result in the introduction of the first generic Carbamazepine 300 mg Extended-Release Capsule product to benefit patients.

Pursuant to 21 CFR 314.50 (d)(v), 21 CFR 314.71 (b), and 21 CFR 314.97, Nostrum hereby submits an exact copy of this submission to the Kansas City District Office.

If you have any questions or comments on this submission, please contact the undersigned at (816) 308-4970 or (b) (6)

Sincerely,

Dhiren N. Shah

Dhiren N. Shah, Ph.D., RAC
Regulatory Affairs
Nostrum Laboratories, Inc.
1800 N. Topping Avenue
Kansas City, MO 64120

Enclosures

cc: Mr. Richard Adams, Deputy Director, Division of Chemistry II (CMC Section only; Desk Copy)
Dr Damaris Maldonado, Team Leader, Division of Chemistry II (CMC Section only; Desk Copy)
Ms. Theresa Liu, Project Manager, Division of Chemistry II (Cover Letter only; Desk Copy)
Ms. Shirley Berryman, New Product Pre-Approval Manager, FDA, KCDO (Field Copy)

NOSTRUM
PHARMACEUTICALS, INC.

505 Thornall St., Suite 304, Edison, NJ 08837 Tel: 732 635 0036 Fax: 732 635 0042

July 16th, 2008

Office of Generic Drugs
Center of Drug Evaluation and Research
Document Control Room (HFD-600)
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

NEW CORRESP
N/45

Attention: Mr. Gary J. Buehler, Director, Office of Generic Drugs

Ref: ANDA 76-697 **Change of Ownership of an Application**
Carbamazepine ER Capsules
300 mg, 200 mg, 100 mg

Pursuant to 21 CFR 314.72(a)(1) the purpose of this submission, in duplicate, is to inform the agency that Nostrum Pharmaceuticals, Inc. (NPI) a/k/a Nostrum Investments, Inc. the owner of Abbreviated New Drug Application 76-697 (ANDA) for Carbamazepine Extended Release Capsules (300 mg, and the more recently amended 200 mg, and 100 mg) has transferred the ownership of the ANDA and all rights to the ANDA to Nostrum Pharmaceuticals, LLC (NPLLC) effective 11/28/2007.

Please note that Nostrum Laboratories Inc. (NLI) remains the site currently seeking manufacturing, testing, and distribution approval of the intended drug product. NLI is a majority owned subsidiary of NPLLC and both entities are under common ownership and control. Pursuant to 21 CFR 201.1(g) the product will use NLI registered labeler code upon approval.

The new owner of the application, NPLLC, assumes the obligations of ownership of the ANDA via a separate submission to the agency through the undersigned who also continues to serve as agent for NPLLC with regard to this ANDA.

Pursuant to 21 CFR 314.96(b) an exact copy of this communication has been sent to the FDA Kansas City District Office.

If you have any questions or comments regarding this submission, please contact the undersigned at 816-308-4970 or 816-841-4634.

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JUL 17 2008
OGD

Simply Better Medicines

Sincerely,

Dhiren N. Shah

Dhiren N. Shah PhD, RAC
Regulatory Affairs
Nostrum, Laboratories, Inc.
1800 N. Topping Avenue
Kansas City, MO 64120

cc: Ms. Shirley Berryman, New Product Pre-Approval Manager, FDA, KCDO (Field Copy)

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ 08837 Tel: 732 635 0036 Fax 732 635 0042

pending 10.1

July 16th, 2008

Office of Generic Drugs
Center of Drug Evaluation and Research
Document Control Room (HFD-600)
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

NEW CORRES
N/XS

Attention: Mr. Gary J. Buehler, Director, Office of Generic Drugs

Ref: ANDA 76-697 **Change of Ownership of an Application**
Carbamazepine ER Capsules
300 mg, 200 mg, 100 mg

Dear Sir,

Pursuant to 21 CFR 314.72(a) (2) the purpose of this submission, in duplicate, is to inform the agency that Nostrum Pharmaceuticals, Inc. (NPI) a/k/a Nostrum Investments, Inc. has transferred ownership of the Abbreviated New Drug Application 76-697 (ANDA) for Carbamazepine Extended Release Capsules (300 mg, and as more recently amended 200 mg, and 100 mg) and all rights to the ANDA to Nostrum Pharmaceuticals, LLC (NPLLC) effective 11/28/2007.

Please note that Nostrum Laboratories Inc. (NLI) remains the site currently seeking manufacturing, testing, and distribution approval of the intended drug product. NLI is a majority owned subsidiary of NPLLC and both entities are under common ownership and control. Pursuant to 21 CFR 201.1(g) the product will use NLI registered labeler code upon approval. NPLLC directly and through NLI will continue to assume all agreements, promises, commitments and conditions made by the former owner NPI and set forth within the ANDA.

The undersigned continues to serve as the authorized agent of the ANDA on behalf of NPLLC and should be contacted if you have any questions regarding this communications and/or the ANDA.

Pursuant to 21 CFR 314.72(a) (2) (iii) NPLLC believes it has acquired an entire copy of the ANDA and its subsequent amendments to date. However, neither NPLLC nor NPI can verify whether an amendment to the ANDA was submitted on Oct 22nd, 2003 in response to the CMC deficiency letter issued Oct 2nd, 2003. A comprehensive reply to the Oct 2nd, 2003

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OGD

deficiency letter was made by NPI on Dec 12th, 2003 and hence we believe that the Oct 2nd, 2003 amendment does not exist and request the agency to confirm the same. If the agency is unable to confirm that the October 2nd, 2003 amendment does not exist, then we request the agency to provide NPLLC, as the new owner of the ANDA, with a copy of the amendment at the agency's earliest opportunity. NPLLC agrees to pay for such as per fee schedule under § 20.45.

Pursuant to 21 CFR 314.96(b) an exact copy of this communication has been sent to the FDA Kansas City District Office.

If you have any questions or comments regarding this submission, please contact the undersigned at 816-308-4970 or by fax at 816-841-4634.

Sincerely,

Dhiren N. Shah Ph.D., RAC
Regulatory Affairs
Nostrum, Laboratories, Inc.
1800 N. Topping Avenue
Kansas City, MO 64120

cc: Ms. Shirley Berryman, New Product Pre-Approval Manager, FDA, KCDO (Field Copy)

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ 08837 Tel: 732 635 0036 Fax 732 635 0042

July 23rd, 2008

ORIG AMENDMENT

Office of Generic Drugs
Center of Drug Evaluation and Research
Document Control Room (HFD-600)
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

N/C

Attention: Mr. Gary Buehler, Director, Office of Generic Drugs

Ref: ANDA 76-697
Carbamazepine ER Capsules
300 mg, 200 mg, 100 mg

Documentation of Receipt of Notice and Filing of Complaint

Dear Sir

Pursuant to 21 CFR 314.95(b) Nostrum Pharmaceuticals, LLC (NPLLC), owner of the Abbreviated New Drug Application 76-697 (ANDA) for Carbamazepine Extended Release Capsules (300 mg, and as more recently amended, 200 mg, and 100 mg), has notified the patent holder and New Drug Application (NDA) holder Shire Laboratories, Inc. (Shire) with a notice of Paragraph IV certification (Notice) for Shire's Carbatrol 200 mg and 100 mg strengths (NDA Number 020712).

Pursuant to 21 CFR 314.96 (e) the purpose of this submission, in duplicate, is to document with the agency, receipt of the Notice by Shire. The return receipts acknowledging receipt of the Notice by Shire are enclosed as Attachment 1.

Pursuant to 21 CFR 314.107(f)(2) NPLLC would also like to inform the agency that on July 2, 2008, Shire filed a complaint for patent infringement against NPLLC in U.S. District Court, District of New Jersey (Civil Action No. 03:08-cv-03309-MLC-TJB) based upon NPLLC's Notice to Shire on its Carbatrol 200 mg and 100 mg strengths. A copy of the complaint as filed by Shire and downloaded from the U.S. District Court; District of New Jersey Official Court Electronic Document Filing System is enclosed as Attachment 2.

Pursuant to 21 CFR 314.96(b) an exact copy of this communication has been sent to the FDA Kansas City District Office.

If you have any questions or comments regarding this submission, please contact the undersigned at 816-308-4970 or by fax at 816-841-4634.

Sincerely,

07-23-2008

For Dr. Shah

Dhiren N. Shah PhD, RAC
Regulatory Affairs
Nostrum, Laboratories, Inc.
1800 N. Topping Avenue
Kansas City, MO 64120

cc: Ms. Shirley J. Berryman, New Product Pre-Approval Manager, FDA, KCDO (Field Copy)

Encl: 1. Attachment 1 Return Receipts for the Notice to Shire
Attachment 2 Shire's Complaint against NPLLC

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 732 635 0042

Sept 3rd, 2008

N-000-AB

Office of Generic Drug
Center of Drug Evaluation and Research
Document Control Room (HFD-600)
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

Attention: Mr. Gary J. Buehler, Director, Office of Generic Drugs

Ref: ANDA #76-697, Carbamazepine ER Capsules 300 mg, 200 mg , 100 mg

Subject: Bioequivalence Amendment

Dear Sir

Pursuant to 21CFR314.96(a)(3) the undersigned on behalf of Nostrum pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI) hereby submits this amendment to ANDA 76-697 in response to the Bioequivalence Deficiency Letter (Attachment 1 to this cover letter) issued by the Division of Bioequivalence (DBE) dated July 31st, 2007.

The purpose of the amendment being filed electronically in eCTD format is to respond to the DBE's July 31st, 2007 Deficiency letter and provide supporting data. Our response to this deficiency letter is available within **Section 3.2.P.5.4**.

As requested by the agency this amendment is being filed electronically in eCTD format. All information is being included within the single sequence "0000" in the root folder "076697"

Should you have any questions, please contact the undersigned at 816-308-4970 or by fax at 816-841-4634.

Sincerely

for Dhiren N. Shah PhD, RAC
Regulatory Affairs
Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120
dshah@nostrumlabs.com

MAJOR AMENDMENT

ANDA 76-697

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Nostrum Pharmaceuticals, Inc. TEL: 816-308-4970

ATTN: Dhiren N. Shah FAX: 816-841-4634

FROM: Theresa Liu PROJECT MANAGER: (301) 827-5791

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-release Capsules USP, 300 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

See attached chemistry comments.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-697 APPLICANT: Nostrum Pharmaceuticals, Inc.

DRUG PRODUCT: Carbamazepine Extended-release Capsules, 300 mg

The deficiencies presented below represent MAJOR deficiencies.

Please be aware that the Office of Generic Drugs uses data generated on the ANDA pivotal batch not only to demonstrate bioequivalence to the Reference Listed Drug, but also as a quality benchmark. Because of the importance of this batch, it is essential that details of its manufacture be unassailable. We acknowledge the changes and emphasis placed in the (b) (4)

As mentioned in previous communications, the apparent (b) (4) renders the original bioequivalence batch as inappropriate for *in-vivo* bioequivalence studies. We reiterate our previous request for submission of a new bioequivalence study as delineated in our last deficiency letter. Please also contact our Division of Bioequivalence for the appropriate *in vivo* bioequivalence study requirements. Should you wish to communicate with the Division by means of a teleconference, please contact the CMC review team project manner Theresa Liu at 301-827-5791 regarding this matter.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Michael S Furness

8/13/2007 08:50:23 AM

BIOEQUIVALENCY AMENDMENT

ANDA 76-697

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Nostrum Pharmaceuticals, Inc. TEL: 816-308-4970

ATTN: Dhiren N. Shah FAX: 816-841-4634

FROM: Keri Suh FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on April 28, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-release Capsules USP, 100 mg, 200 mg and 300 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76697

APPLICANT: Nostrum Pharmaceuticals Inc

DRUG PRODUCT: Carbamazepine Extended Release Capsules, 100 mg, 200 mg and 300 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. The dissolution testing is incomplete. Please repeat dissolution testing using the following FDA-recommended dissolution method for all three strengths:

Apparatus:	USP Apparatus 2 (paddle)	
Rotation speed	75 rpm	
Medium	**Temperature**: 37°C	**Volume**
First 4 hours;	Dilute acid, pH 1.1 with 1.8 % B-cyclodextrin	600 mL
After 4 hours	50 mM Phosphate Buffer, pH 7.5 with 1.1 % B cyclodextrin	1000 mL
Sampling times	**1, 2, 4, 8 and 10 hours.**	

The method is posted on the FDA dissolution website

2. Please conduct dissolution testing in three additional media (0.1N HCl, acetate buffer pH 4.5 and phosphate buffer 6.8) for the highest strength, 300 mg, per CDER 2003 BA/BE Guidance for modified release drug products.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit

7/31/2008 07:36:51 PM

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 732 635 0042

Sept 24th, 2008

Office of Generic Drug
Center of Drug Evaluation and Research
Document Control Room (HFD-600)
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

Attention: Mr. Gary J. Buehler, Director, Office of Generic Drugs

Ref: ANDA #76-697, Carbamazepine ER Capsules 300 mg, 200 mg, and 100 mg

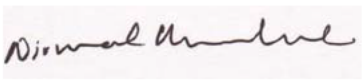
Subject: Change of Agent

Dear Sir

Effective submission of this communication, the Regulatory Agent for Nostrum's Carbamazepine ER Capsules 300 mg, 200 mg, and 100 mg ANDA # 76-697 will be:

Theodore (Ted) R. Miro
Regulatory Agent/VP of Quality Systems
Nostrum Laboratories, Inc.
Mailing Address: 1800 N Topping Ave
Kansas City MO 64120
Tel: 732 635 0036 ext 102
Fax: 816 841 4634
Email: ted@nostrumpharma.com

Sincerely



Nirmal Mulye PhD
President
Nostrum Pharmaceuticals, LLC

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 732 635 0042

Sept 25th, 2008

Office of Generic Drug
Center of Drug Evaluation and Research
Document Control Room (HFD-600)
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

Attention: Mr. Gary J. Buehler, Director, Office of Generic Drugs

Ref: ANDA #76-697, Carbamazepine ER Capsules 300 mg, 200 mg, and 100 mg

Subject: Change of Contact/Agent
Labeling Amendment (PDF copy of the Labeling)
Bioequivalency Request Response

Dear Sir

Pursuant to 21CFR314.96(a)(3) the undersigned on behalf of Nostrum Pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI) and in response to the DBE telephone request on September 18, 2008, hereby submits this amendment to ANDA 76-697.

The purpose of the amendment being filed electronically in eCTD format is:

1. Change of contact/agent for this ANDA as available within **Section 1.3.1.2**.
2. Provide a PDF copy of the package insert that was omitted from our April 28th, 2008 submission within **Section 1.14.2.2**. For your convenience a copy of the prescribing information in SPL format is also provided here.
3. Provide dissolution data on the Reference Listed Drug (RLD) Carbatrol® as requested by the agency. Such information is available within **Section 3.2.P.5.4**.

This amendment is being filed electronically in eCTD format. All information is being included within the single sequence "0001" in the root folder "076697"

Should you have any questions, please contact the undersigned at 816-308-4902 or by fax at 816-308-4975.

Sincerely

Himanshu Sud

RA Manager

for

Theodore (Ted) R. Miro
Regulatory Agent/VP of Quality Systems
Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120
ted@nostrumpharma.com

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 732 635 0042

October 10, 2008

Mr. Gary J. Buehler, Director
Office of Generic Drug
Center for Drug Evaluation and Research
Document Control Room (HFD-600)
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

UNSOLICITED AMENDMENT - CHEMISTRY

Re: ANDA #76-697, Carbamazepine ER Capsules 300 mg, 200 mg, and 100 mg

Subject: CMC Amendment; Residual Solvent Information and Updated Stability Data

Dear Mr. Buehler,

Pursuant to 21CFR314.96(a)(3) the undersigned on behalf of Nostrum pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI) hereby submits this amendment to ANDA 76-697.

The purpose of the amendment being filed electronically in eCTD format is:

1. Provide residual solvent information on the drug substance, excipients, and the drug product along with supporting information within **Section 3.2.P.5.4**.
2. Provide updated specifications for the drug substance within **Section 3.2.S.4.1** with the following changes:

    a. (b) (4) the limits of residual solvents to conform to the drug substance manufacturer, as follows:

Residual Solvent	From:	To:
(b) (4)		

b. Revised the related compounds specification by (b) (4) to comply with the drug substance manufacturer, as follows:

Related compounds	From:	To:
	(b) (4)	

3. Provide updated specifications (to include residual solvent information) for the drug product within **Section 3.2.P.5.1**. and test method within Section 3.2.P.5.2.

4. Provide updated stability data on the drug product within **Section 3.2.P.8**.

This amendment is being filed electronically in eCTD format. All information is being included within the single sequence "0002" in the root folder "076697".

Should you have any questions, please contact the undersigned at 816-308-4902 or by fax at 816-308-4975.

Sincerely

Himanshu Sud
RA Manager
for
Theodore (Ted) R. Miro
Regulatory Agent/VP of Quality Operations
Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120
ted@nostrumpharma.com

BIOEQUIVALENCE AMENDMENT

ANDA 76-697

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Nostrum Pharmaceuticals, Inc. TEL: 816-308-4970

ATTN: Dhiren N. Shah FAX: 816-841-4634

FROM: Christina Thompson FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on March 26, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-release Capsules USP, 300 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 76697

APPLICANT: Nostrum Pharmaceuticals LLC

DRUG PRODUCT: Carbamazepine Extended-Release Capsules
100 mg, 200 mg and 300 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Based on the submitted data, DBE recommends the following dissolution method and specifications for your test product:

Apparatus:	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm
Medium	
First 4 hours:	Dilute acid, pH 1.1 with 1.8% β-cyclodextrin, 600 mL
After 4 hours:	50 mM Phosphate Buffer, pH 7.5 with 1.1% β-cyclodextrin, 1000 mL
Sampling Times	1, 2, 4, 8 and 10 hours
Specifications	**300 mg** strength: 1hr: (b) (4)%; 4 hr: (b) (4)%; 8 hr: NLT (b) (4)% **100 mg and 200 mg** strengths: 1hr: (b) (4)%; 4 hr: (b) (4)%; 8 hr: NLT (b) (4)%

With your response, please indicate if you accept the above FDA-recommended dissolution method and specifications.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit

10/23/2008 04:57:03 PM

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 816 308 4975

November 22, 2008

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Ref: ANDA #76-697, Carbamazepine ER Capsules 300 mg, 200 mg, and 100 mg

Subject: "Bioequivalence and Chemistry Amendment"

Dear Mr. Buehler,

Pursuant to 21 CFR 314.96, the undersigned, on behalf of Nostrum Pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI), hereby submits this amendment to our pending application in response to the DBE Deficiency letter dated October 23, 2008 (Attachment1). Reference is also made to the telephone conversation on November 6, 2008 with Aaron Siegler, Project Manager at DBE, during which it was clarified that the sampling time points at 2 hours and 10 hours are for information only.

In addition, we are providing revised finished product and stability specifications and method to reflect the DBE recommended dissolution method and specifications. Also provided are updated stability data.

DBE Deficiency 1:

Based on the submitted data, DBE recommends the following dissolution method and specifications for your test product:

Apparatus:	**USP Apparatus 2 (paddle)**
Rotation Speed	**75 rpm**
Medium	
First 4 hours:	**Dilute acid, pH 1.1 with 1.8% β–cyclodextrin, 600 mL**
After 4 hours	**50 mM Phosphate Buffer, pH 7.5 with 1.1% β–cyclodextrin, 1000 mL**
Sampling Times	**1, 2, 4, 8, 10 hours**
Specifications	**300 mg strength:** **1 hr: (b) (4)%; 4 hr: (b) (4)%; 8hr: NLT (b) (4)%** **100 mg and 200 mg strengths:** **1 hr: (b) (4)%; 4 hr: (b) (4)%; 8hr: NLT (b) (4)%**

NLI Response to DBE Deficiency 1:

NLI accepts DBE's recommended method and specifications for its Carbamazepine ER Capsules 300 mg, 200 mg, and 100 mg, with the exception of sampling times as listed in the table below:

Apparatus:	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm
Medium	
First 4 hours:	Dilute acid, pH 1.1 with 1.8% β–cyclodextrin, 600 mL
After 4 hours	50 mM Phosphate Buffer, pH 7.5 with 1.1% β–cyclodextrin, 1000 mL
Sampling Times	1, 4, 8 hours; 10 hours (10 hours for internal information only)
Specifications	300 mg strength: 1 hr: (b) (4)%; 4 hr (b) (4)%; 8hr: NLT (b) (4)% 100 mg and 200 mg strengths: 1 hr: (b) (4)%; 4 hr: (b) (4)%; 8hr: NLT (b) (4)%

Please note that based on the clarification during the above-mentioned telephone communication with the Agency, NLI removed the sampling time at 2 hours and maintained the 10 hours sampling time only for internal information and records.

In addition, NLI provides for the Chemistry Division, updated in process specifications within **Section 3.2.P.3.4**, revised finished product specifications and stability specifications within **Section 3.2.P.5.1**, and test method for finished product within **Section 3.2.P.5.2**, to reflect the newly adopted DBE's dissolution recommendations.

NLI also provides the updated 12 month RT stability data for its submissions batches where the dissolution data has been generated per the above method and to the above specifications. The stability data is available within **Section 3.2.P.8**.

This amendment is being filed electronically in eCTD format. All information is being included within the single sequence "0003" in the root folder "076697".

Should you have any questions, please contact the undersigned at 816-308-4902 or by fax at 816-308-4975.

Sincerely

Himanshu Sud

RA Manager

(for)

Theodore (Ted) R. Miro
Regulatory Agent/VP of Quality Systems
Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120
ted@nostrumpharma.com

COMPLETE RESPONSE -- MINOR

ANDA 76-697

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Nostrum Pharmaceuticals, LLC. TEL: 816-308-4902

ATTN: Theodore R. Miro FAX: 816-308-4975

FROM: Lisa Kwok FDA CONTACT PHONE: 240-26-8494

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-release Capsules, 100 mg, 200 mg and 300 mg.

Reference is also made to your amendments dated April 28, October 10, and November 24, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__4__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Following this page, 3 pages withheld in full - (b)(4)

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

/s/

Aloka Srinivasan
12/15/2008 10:12:42 AM
for Vilayat A. Sayeed, Ph.D.

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 816 308 4975

January 15, 2009

Vilayat A. Sayeed, PhD
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

EXPEDITED REVIEW REQUESTED

Ref: ANDA #76-697, Carbamazepine ER Capsules 300 mg, 200 mg, and 100 mg
Subject: "CMC Minor Amendment"

Dear Dr Sayeed,

Pursuant to 21 CFR 314.96, the undersigned, on behalf of Nostrum Pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI), hereby submits this amendment to our pending application in response to the CMC Minor Deficiency letter dated December 15, 2008 (Attachment 1).

Reference is also made to the telephone conversation on December 18, 2008, with Dr. Aloka Srinivasan, Team Leader, and Dr. Latiff Hussain, Chemist Reviewer, of OGD, during which NLI was provided clarification on several deficiency items.

Our responses to the deficiencies cited are listed below:

A. Deficiencies:

1. *The Drug Master File # (b) (4) is deficient and the holder has been notified. Please do not respond until the DMF holder has responded to the deficiencies.*

NLI Response to Deficiency A.1:

NLI has been informed by (b) (4), the holder of DMF # (b) (4) that they have responded to their deficiencies on December 24, 2008. A copy of their response cover letter is provided here as **Attachment 2**. In addition, provided in Attachment 3, is a Letter of Commitment from (b) (4) in which they have agreed to provide NLI with a custom-specification for the (b) (4) with a limit of (b) (4).

Following this page, 8 pages withheld in full - (b)(4)

(b) (4). NLI has been inspected by the agency on three occasions in 2008, while (b) (4) was last inspected by the agency in (b) (4).

10. *We request you to provide an electronic copy, in addition to the paper copy, of the summary of response to the agency's questions, provided in this deficiency letter. The relevant attachments and the body data related to the amendment may be submitted in the same format as your original application.*

NLI Response to B.10:

This amendment is being filed electronically in eCTD format. All information is being included within the single sequence "0004" in the root folder "076697".

Should you have any questions, please contact the undersigned at 816-308-4902 or by fax at 816-308-4975.

Himanshu Sud
RA Manager
(for)
Theodore (Ted) R. Miro
Regulatory Agent/VP of Quality Systems
Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120
ted@nostrumpharma.com

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 816 308 4975

March 26, 2009

Gary Buehler
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

TELEPHONE AMENDMENT - CHEMISTRY

Re: ANDA #76-697 Carbamazepine ER Capsules, 300 mg, 200 mg, and 100 mg

Dear Mr. Buehler:

Pursuant to 21 CFR 314.96, the undersigned, on behalf of Nostrum Pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI), hereby submits this telephone amendment to our pending ANDA # 76-697 in response to the Agency's correspondence dated March 17, 2009 (**Attachment 1**). Reference is also made to the telephone conversation on March 19, 2009, with Dr. Aloka Srinivasan and Dr. Latiff Hussain of OGD, during which clarification was provided with regards to required testing related to Deficiency 1 (outlined below).

MINOR Deficiencies- Chemistry:

Deficiency 1:

(b) (4) *Hence please demonstrate the specificity of the* (b) (4) *procedure.*

NLI Response:

NLI performed additional validation work to demonstrate the specificity of the (b) (4) procedure for (b) (4)

Following this page, 1 page withheld in full - (b)(4)

NLI's Response:

NLI's has revised the stability protocols for Carbamazepine ER Capsules, 100 mg, 200 mg and 300 mg, to reflect a tentative expiration date of 24 months (2 yrs). The revised stability protocols are available within **Section 3.2.P.8.2**.

With this response, NLI's hope that the two outstanding concerns that OGD submitted on March 17, 2009, have been sufficiently addressed and looks forward to ANDA approval.

This amendment is being filed electronically in eCTD format with all content within sequence "0005" in the root folder "076697".

Should you have any questions, please contact the undersigned at 816-308-4902 or by fax at 816-308-4975.

Thank you,

Himanshu Sud
RA Manager
(for)
Theodore (Ted) R. Miro
Regulatory Agent/VP of Quality Systems
Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120
ted@nostrumpharma.com

CC: Via facsimile to:
Aloka Srinivasan and Latiff Hussain: 1-240-276-8474

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 76-697

Nostrum Laboratories, Inc.
U. S. Agent for: Nostrum Pharmaceuticals, LLC
Attention: Dhiren N. Shah, Ph.D., RAC
1800 North Topping Avenue
Kansas City, MO 64120

Dear Sir:

We acknowledge receipt of your communication dated July 16, 2008, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for the abbreviated new drug application (ANDA) for Carbamazepine Extended-release Capsules USP, 100 mg, 200 mg, and 300 mg.

Your letter details the transfer of ownership of the ANDA from Nostrum Pharmaceuticals, Inc. to Nostrum Pharmaceuticals, LLC.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the pending application.

The material submitted is being retained as part of your application.

Sincerely yours,

{See appended electronic signature page}

William P. Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Timothy W. Ames
4/27/2009 11:13:23 AM
Signing for Wm. Peter Rickman

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 816 308 4975

May 23, 2009

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

Ref: ANDA #76-697, Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg

Subject: Patent Amendment – Status of Litigation
Change of Contact/Agent

Dear Mr. Buehler,

Pursuant to 21 CFR 314.96, the undersigned, on behalf of Nostrum Pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI) - collectively Nostrum, hereby submits this amendment to the above-referenced pending ANDA in response to a May 21, 2009 request from Martin Shimer of the Office of Generic Drugs. Reference is also made to the May 22, 2009 telephone conversation with Mr. Shimer. Specifically, Nostrum was asked to provide for a litigation status update on ANDA 76-697 for Carbamazepine ER Capsules, 100 mg, 200 mg and 300 mg.

Currently, there are two pending litigations in U.S. District Court, District of New Jersey (Trenton) between Shire LLC and Nostrum Pharmaceuticals, LLC relating to ANDA 76-697:

1. Civil Action No. 3:2003cv04436 filed on 09/18/03 for Carbamazepine ER Capsules, 300 mg; and
2. Civil Action No. 8:2008cv03309 filed on 07/02/08 for Carbamazepine ER Capsules, 100 mg and 200 mg.

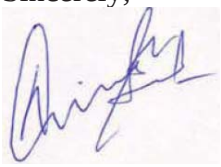
Resolution has not yet been reached in either of these actions.

In addition, updated information for the new Contact/Agent for this ANDA is enclosed within **Section 1.3.1.2**.

This amendment is being filed electronically in eCTD format. All information is included in sequence "0006" in the root folder "076697".

If you have any questions, please contact the undersigned at (732) 603-1228 or via facsimile at (816) 308-4975.

Sincerely,



Himanshu Sud
RA Manager
(for)
Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 816 308 4975

May 25, 2009

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

REF: ANDA #76-697 Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg

SUBJECT: Labeling Amendment

Dear Mr. Buehler:

Pursuant to 21 CFR 314.96 (a) (1), the undersigned, on behalf of Nostrum Pharmaceuticals, LLC and Nostrum Laboratories, Inc. (NLI), submits this labeling amendment to pending ANDA #76-697 for consistency with the Reference Listed Drug (RLD), Carbatrol®, which was updated with additions for safety- related issues on May 5, 2009. Reference is also made to the telephone conversation on May 6, 2009, with Charles Hoppes, Labeling Reviewer, who requested us to revise our labeling for Carbamazepine ER Capsules as per the recent updates to the RLD labeling.

The purpose of this amendment is to provide for:

1. Updated draft labeling within **Section 1.14.1.3**, along with a side by side comparison for the inserts within **Section 1.14.3.1**. The Structured Product Labeling (SPL) for the same is available **here**.

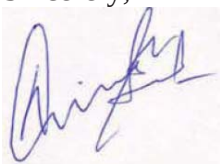
The Drug Information Update posted by CDER on May 5, 2009, requires manufacturers of anti-epileptic drugs (AED) or anticonvulsant drugs to update product labeling with a warning about the increased risk of suicidal thoughts or actions and develop a medication guide to help patients understand this risk, and to include language pertaining to the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

At this time, NLI has updated the package insert labeling (only) according to the RLD changes (in line with the above), as the medication guide is yet to be made available by the RLD holder. NLI will update its labeling (for Carbamazepine ER Capsules) with the medication guide upon its availability.

This amendment is being filed electronically in eCTD format. All information is included in sequence "0007" in the root folder "076697".

If you have any questions, please contact the undersigned at (732)603-1228 or via facsimile at (816)308-4975.

Sincerely,



Himanshu Sud
RA Manager
(for)
Zoia Ploscaru,
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

Telephone Fax

ANDA 76-697

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8976

TO: Nostrum Pharmaceuticals, Inc.

TEL: 816-308-4902

ATTN: Zoia Ploscaru

FAX: 816-308-4975

FROM: LCDR. Melaine Shin, R.Ph
Labeling Reviewer

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-Release Capsules.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments: **See the attachment**

Please send me an email confirming the receipt of this letter with your ANDA number in the Subject field.

Email: melaine.shin@fda.hhs.gov

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-697

Dates of Submissions: May 25, 2009

Applicant's Name: Nostrum Pharmaceuticals, Inc.

Established Name: Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg

Proposed Proprietary Name: None

LABELING DEFICIENCIES:

GENERAL:

- Revise the storage temperature recommendation as follows:

  "Store at 20°-25° (68° – 77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]"

CONTAINER – 30s and 120s for 100 mg, 200 mg, and 300 mg.

- See comment under GENERAL.

PROFESSIONAL INSERT:

- Please note that the only 300 mg strength is eligible for full approval. In order to approve the 300 mg strength, we ask that you remove reference to 100 mg and 200 mg strengths from your insert labeling.

- See comment under GENERAL.

Please revise your labeling, as instructed above, and submit electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lillie Golson
5/29/2009 04:23:12 PM
Lillie Golson for Wm. Peter Rickman

NOSTRUM
PHARMACEUTICALS, LLC

505 Thornall St., Suite 304, Edison NJ Tel: 732 635 0036 Fax 816 308 4975

June 10, 2009

Wm. Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773

RE: ANDA #76-697 Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg Labeling Amendment

Dear Mr. Rickman:

Pursuant to 21 CFR 314.96 (a) (1), the undersigned, on behalf of Nostrum Pharmaceuticals, LLC and Nostrum Laboratories, Inc. (NLI), submits this Labeling Amendment to pending ANDA #76-697 in response to the enclosed Labeling Deficiency Letter dated May 29, 2009 (**Attachment 1**). Reference is also made to subsequent communication with Melaine Shin, R.Ph, Labeling Reviewer, for providing clarification in resolving the labeling deficiencies.

The purpose of this amendment is to address the following Agency comments on labeling:

1. *GENERAL*
   - *Revise the storage temperature recommendation as follows: "Store at 20˚-25˚ (68˚-77˚F); excursions permitted to 15˚-30˚C (59˚-86˚F) [See USP Controlled Room Temperature]"*

NLI Response:
The Container Closure Labels and the Package Insert have been updated to reflect the above storage conditions. Updated Container Closures are available within **Section 1.14.2.1**, and updated Professional Insert (PI) is available within **Section 1.14.2.2.**

2. *CONTAINER – 30s and 120s for 100 mg, 200 mg, and 300 mg*
   - *See comment under GENERAL*

NLI Response:
Updated Container Closures are available within **Section 1.14.2.1.**

3. *PROFESSIONAL INSERT*

- *Please note that the only 300 mg strength is eligible for full approval. In order to approve the 300 mg strength, we ask that you remove reference to 100 mg and 200 mg strengths from your insert labeling.*
- *See comment under GENERAL*

To facilitate the review of your next submission, and in accordance with 21 CFR314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your proposed labeling with all differences annotated and explained.

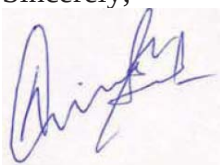
NLI Response:

Updated PI is available within **Section 1.14.2.2** and the Structured Product Labeling (SPL) for the same is available **here**. The updated side-by-side comparison for the insert is available within **Section 1.14.3.1**.

This amendment is being filed electronically in eCTD format. All information is included in sequence "0008" in the root folder "076697".

If you have any questions, please contact the undersigned at (732) 603-1228 or via facsimile at (816) 308-4975.

Sincerely,



Himanshu Sud
Regulatory Affairs Manager
(for)
Zoia Ploscaru,
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

NOSTRUM
PHARMACEUTICALS, LLC

July 20, 2009

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT- CHEMISTRY

Ref: ANDA # 76-697, Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg

Dear Mr. Buehler,

Pursuant to 21 CFR 314.96, the undersigned, on behalf of Nostrum Pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI), hereby submits this Telephone Amendment to our pending ANDA in response to the Agency's correspondence dated July 14, 2009 (**Attachment 1**). Reference is also made to the telephone conversation on July 15, 2009, with Dr. Aloka Srinivasan of OGD, during which we have requested clarification regarding the Agency's comments as Nostrum has already addressed two of the three comments in previous submissions. Dr. Srinivasan recommended that we respond to the current comments with references and copies of the old submissions.

MINOR Deficiencies- Chemistry

Comment 1:

Please explain and interpret in detail the in-process specifications for (b) (4) of the (b) (4). Also, the specifications for (b) (4) should be (b) (4) based on the observed data.

Response:

(b) (4)

The specification was designed based on the understanding of the process, the statistical

Following this page, 3 pages withheld in full - (b)(4)

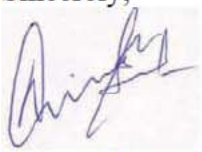
(b) (4)

With the above responses, NLI believes that we have sufficiently addressed your comments.

This amendment is being filed electronically in eCTD format. All information is being included within the single sequence "0009" in the root folder "076697".

If you have any questions, please contact the undersigned at (732) 603-1228 or via facsimile at (816) 308-4975.

Sincerely,



Himanshu Sud
RA Manager
(for)
Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

CC via Facsimile to: Latiff Hussain, Chemist Reviewer, at: 240-276-8474
Lisa Kwok, Project Manager, at: 240-276-8474

NOSTRUM
PHARMACEUTICALS, LLC

August 17, 2009

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT- CHEMISTRY

Ref: ANDA # 76-697, Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg

Dear Mr. Buehler,

Pursuant to 21 CFR 314.96(a)1, the undersigned, on behalf of Nostrum Pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI), hereby submits this Telephone Amendment to our pending ANDA in response to the Agency's correspondence dated August 5, 2009 (**Attachment 1**). References are made to the telephone conversations on August 6, 7 and 11, 2009, with Dr. Latiff Hussain, Chemist Reviewer at OGD, during which the discussions covered NLI's intention to (b) (4) the bio/stability batch size with the necessary documentation to support this change, and the Agency's recommendation that NLI employ the (b) (4) and provide data using this method. In addition, NLI was requested to provide updated CRT stability data for the exhibit/submission batches. Further details of the above-mentioned discussions are provided below.

MINOR Deficiencies- Chemistry

Comment 1:
On page 472 of the April 28, 2008 amendment, you stated that the (b) (4) Please clarify. Also, on page 481 the theoretical (b) (4) . Please clarify.

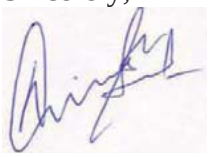
Following this page, 2 pages withheld in full - (b)(4)

We believe that we have sufficiently addressed all of the Agency's comments, and hence, expect that an approval of this application will be issued soon by the Agency.

This amendment is being filed electronically in eCTD format. All information is being included within the single sequence "0010" in the root folder "076697".

If you have any questions, please contact the undersigned at (732) 603-1228 or via facsimile at (816) 308-4975.

Sincerely,



Himanshu Sud
RA Manager
(for)
Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

CC via Facsimile: Lisa Kwok, Project Manager, at: 240-276-8474

NOSTRUM
PHARMACEUTICALS, LLC

September 3, 2009

Gary J. Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT- CHEMISTRY

Ref: ANDA # 76-697, Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg

Dear Mr. Buehler,

Pursuant to 21 CFR 314.96(a)(1), the undersigned, on behalf of Nostrum Pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI), hereby submits this Telephone Amendment to our pending ANDA in response to the Agency's comments provided during the telephone conversations on August 27, 2009, September 1 and 2, 2009, between Dr. Latiff Hussain, Chemist Reviewer at OGD, and Zoia Ploscaru of NLI.

NLI addresses below the Agency's comments:

Comment 1
In the manufacturing process, (b) (4) .

Response
NLI agreed to the Agency's recommendation and will (b) (4) for all three strengths provided in Section **3.2.P.3.3**.

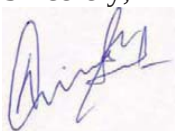
Comment 2
Add a specification of (b) (4) **, which should be reflective of the obtained data. The specifications for the other** (b) (4) **should be** (b) (4) **as per the obtained data.**

Response
NLI has revised the in-process specifications for the (b) (4) to include a specification for the (b) (4) and also to (b) (4) the specifications for the other (b) (4) as shown in the table below:

Following this page, 1 page withheld in full - (b)(4)

If you have any questions, please contact the undersigned at (732) 603-1228 or via facsimile at (816) 308-4975.

Sincerely,



Himanshu Sud
RA manager
(for)
Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

CC via Facsimile to: Latiff Hussain Ph.D., Chemist Reviewer, at: 240-276-8474

NOSTRUM
PHARMACEUTICALS, LLC

Sept 29, 2009

Wm. Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773

RE: ANDA #76-697 Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg
Labeling Amendment

Dear Mr. Rickman:

Pursuant to 21 CFR 314.96 (a) (1), the undersigned, on behalf of Nostrum Pharmaceuticals, LLC and Nostrum Laboratories, Inc. (NLI), submits this Labeling Amendment per the Agency's request on September 29, 2009 to revise the "Food Effect" section of its Prescribing Information to read:

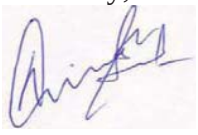
Food Effect:
The multiple dose study conducted in the fed state showed that the steady-state Cmax values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

Updated PI is available within **Section 1.14.2.2** and the Structured Product Labeling (SPL) for the same is available **here**. The updated side-by-side comparison for the insert is available within **Section 1.14.3.1**.

This amendment is being filed electronically in eCTD format. All information is included in sequence "0012" in the root folder "076697".

If you have any questions, please contact the undersigned at (732) 603-1228 or via facsimile at (816) 308-4975.

Sincerely,



Himanshu Sud
Regulatory Affairs Manager
(for) **Zoia Ploscaru,**
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
zploscaru@nostrumlabs.com

NOSTRUM
PHARMACEUTICALS, LLC

Oct 6, 2009

Wm. Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773

RE: ANDA #76-697 Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg
Labeling Amendment

Dear Mr. Rickman:

Pursuant to 21 CFR 314.96 (a) (1), the undersigned, on behalf of Nostrum Pharmaceuticals, LLC and Nostrum Laboratories, Inc. (NLI), submits this Labeling Amendment per the Agency's request on Oct 6, 2009 to revise the "Food Effect" section of its Prescribing Information for 100 mg, and 200 mg strength to read:

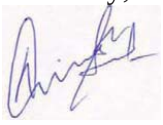
Food Effect:
The multiple dose study conducted in the fed state showed that the steady-state Cmax values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

Updated PI is available within **Section 1.14.2.2** and the Structured Product Labeling (SPL) for the same is available **here**. The updated side-by-side comparison for the insert is available within **Section 1.14.3.1**.

This amendment is being filed electronically in eCTD format. All information is included in sequence "0013" in the root folder "076697".

If you have any questions, please contact the undersigned at (732) 603-1228 or via facsimile at (816) 308-4975.

Sincerely,



Himanshu Sud
Regulatory Affairs Manager
(for) **Zoia Ploscaru,**
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
zploscaru@nostrumlabs.com

NOSTRUM
PHARMACEUTICALS, LLC

December 15, 2009

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Notification of Change in Contact Phone Number

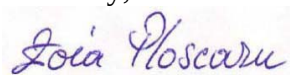
Re: ANDA 76-697 Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg

Dear Mr. Buehler,

Please note that effective December 15, 2009 the new phone number for Zoia Ploscaru, Regulatory Agent and contact person for the above referenced ANDA is **732-993-6210**. The fax number and email address remain the same.

This submission is being filed electronically in eCTD format within sequence "0014" in the root folder "076697".

Sincerely,



Zoia Ploscaru
Regulatory Agent for NPLLC
Sr. Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 N Topping Ave
Kansas City, MO 64120

Tel: 732-993-6210
Fax: 816-308-4975
Email: zploscaru@nostrumlabs.com

Simply Better Medicines

NOSTRUM
PHARMACEUTICALS, LLC

11D Jules Lane, New Brunswick, NJ 08901 Telephone: 732 543 2440 Fax: 732 246 7215

April 20, 2010

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

Ref: ANDA # 76-697 Carbamazepine ER Capsules, 100 mg, 200 mg, and 300 mg
Subject: Patent Amendment – Outcome of Patent Litigation

Dear Mr. Buehler,

Pursuant to 21 CFR 314.96, the undersigned, on behalf of Nostrum Pharmaceuticals, LLC (NPLLC) and Nostrum Laboratories, Inc. (NLI), referred herein as "Nostrum", hereby submits this amendment to the above-referenced pending ANDA to provide information concerning patents litigation related to Carbamazepine ER Capsules, 100 mg, 200 mg and 300 mg, ANDA 76-697. As stated in previously submitted patent amendments toward this ANDA, two separate law suits were filed by Shire in the U.S. District Court, District of New Jersey (Trenton), as follows: Civil Action No. 3:2003cv04436, filed on 9/18/03 for 300 mg strength, and Civil Action No. 8:2008cv03309, filed on 7/2/08, for 100 mg and 200 mg strengths.

At this time, we hereby inform the Agency that said litigations have been settled as reflected in the following documents provided herein:

1) Consent judgment for Civil Action No. 03-4436, dated March 22, 2010
2) Consent judgment for Civil Action No. 08-03309, dated March 22, 2010
3) Shire's letter submitted to the Office of Generic Drugs (OGD), "Re: Carbatrol® (Carbamazepine); Settlement of Paragraph IV Litigation" dated April 12, 2010

As stated in all of the above documents, Shire and Nostrum have entered into a settlement agreement, under which Shire has granted Nostrum a license to '570 patent and '013 patent, effective October 1, 2010, for all three strengths. The agreement does not impact Nostrum's Paragraph IV certifications for the above patents, which are maintained for this ANDA.

In addition, as required by Medicare Modernization Act of 2003, section 1112(a), the Federal Trade Commission (FTC) was notified about the agreement between Shire and Nostrum. The relevant confirmation letter from FTC is included.

This information is submitted to complete the review of this ANDA.

This amendment is being filed electronically in eCTD format. All information is included in sequence "0015" in the root folder "076697".

If you have any questions, please contact the undersigned at (732) 993-6210 or via facsimile at (816) 308-4975.

Sincerely,

Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

September 8, 2010

This Complete Response communication concludes with the following paragraph:

The file on this application is now closed. You are required to take an action described under 21CFR 314.120 which will either amend or withdraw this application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

The reference to 314.120 is incorrect. (It was correct 2 years ago, but was removed from the CFR when the Complete Response rule was finalized, and new 314.110 took its place.) The proper reference is **314.110(b)**.

This communication is being maintained in the DARRTS archive, its attributes changed to Advice, as it was mailed to the firm. A corrected communication has been entered and backdated to July 19, 2010 to maintain the original action date.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 076697

Nostrum Pharmaceuticals, LLC
Attention: Zoia Ploscaru
Contact/Agent
1800 N. Topping Avenue
Kansas City, MO 64120

Dear Madam:

This is in reference to your abbreviated new drug application dated March 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg.

Reference is also made to your amendments dated January 19, February 23, 2004; September 25, 2008; and January 15, March 26, May 25, June 10, July 20, August 17, September 3, September 29, and October 6, 2009.

We have completed the review of your application and have determined that we cannot approve this application in its present form because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, or holding of Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg by Nostrum Laboratories located at 1800 N. Topping Avenue Kansas City, MO 64120 comply with current good manufacturing practice (cGMP) regulations.

Our conclusion is based upon the findings revealed during an inspection of Nostrum Laboratories conducted from October 22 to November 14, 2008 by representatives of the United States Food and Drug Administration and the cGMP Warning Letter issued April 27, 2009. Upon review of this report and the inspectional observations noted during this inspection, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time that you can demonstrate to the Agency that the problems have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

You should amend this application when the cGMP-related issues have been satisfactorily resolved. Your amendment to the application submitted in response to this not approvable letter will be considered a MINOR AMENDMENT provided that the amendment contains no significant additional information necessary to remedy the cGMP problems, and includes a statement from a responsible corporate official certifying that your facilities have been found to be in compliance with cGMPs and have been cleared for approval of the drug product by representatives of the local FDA District Office. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise

your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT. Your amendment should be plainly marked as such in your cover letter.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE

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

/s/

VILAYAT A SAYEED
07/19/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 076697

Nostrum Pharmaceuticals, LLC
Attention: Zoia Ploscaru
Contact/Agent
1800 N. Topping Avenue
Kansas City, MO 64120

Dear Madam:

This letter corrects our letter dated July 19, 2010 in which the Code of Federal Regulations (CFR) citation that was incorrect. This letter serves as the official document, retaining the effective date of July 19, 2010.

This is in reference to your abbreviated new drug application dated March 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg.

Reference is also made to your amendments dated January 19, February 23, 2004; September 25, 2008; and January 15, March 26, May 25, June 10, July 20, August 17, September 3, September 29, and October 6, 2009.

We have completed the review of your application and have determined that we cannot approve this application in its present form because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, or holding of Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg by Nostrum Laboratories located at 1800 N. Topping Avenue Kansas City, MO 64120 comply with current good manufacturing practice (cGMP) regulations.

Our conclusion is based upon the findings revealed during an inspection of Nostrum Laboratories conducted from October 22 to November 14, 2008 by representatives of the United States Food and Drug Administration and the cGMP Warning Letter issued April 27, 2009. Upon review of this report and the inspectional observations noted during this inspection, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time that you can demonstrate to the Agency that the problems have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

You should amend this application when the cGMP-related issues have been satisfactorily resolved. Your amendment to the application submitted in response to this not approvable letter will be considered a MINOR AMENDMENT provided that the amendment contains no significant additional information necessary to remedy the cGMP problems, and includes a

statement from a responsible corporate official certifying that your facilities have been found to be in compliance with cGMPs and have been cleared for approval of the drug product by representatives of the local FDA District Office. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT. Your amendment should be plainly marked as such in your cover letter.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.110(b) which will either amend or withdraw this application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-76697	ORIG-1	NOSTRUM PHARMACEUTICALS INC	CARBAMAZEPINE

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

/s/

VILAYAT A SAYEED
07/19/2010

-----Original Message-----
From: Shimer, Martin
Sent: Monday, February 07, 2011 12:53 PM
To: West, Robert L
Cc: Rickman, William P; Read, David T; Ames, Timothy W; Yang, Steven
Subject: RE: Change in classification - Nostrum Laboratories

Once we are absolutely sure when the Nostrum site is going to be acceptable we'll need to [redacted] (b) (4) This could mean the difference between approving all three strengths in the Nostrum ANDA or just the 300 mg strength.

Marty

-----Original Message-----
From: West, Robert L
Sent: Monday, February 07, 2011 12:49 PM
To: Gooen, Tara
Cc: Yang, Steven; Hussain, Latiff; Shimer, Martin; Rickman, William P; Read, David T
Subject: FW: Change in classification - Nostrum Laboratories

F.Y.I. -

Re: Nostrum's ANDA 76-697 for Carbamazepine Extended-release Capsules. We issued a not-approvable (based upon cGMPs) to the applicant on 7/19/10.

There is still a "withhold" recommendation in EES for this ANDA based upon Nostrum's drug product manufacturing site. It is unclear when the change to acceptable will occur.

Steven: Nevertheless, in anticipation of a favorable response for the Nostrum site, some of the other facilities appear to be out of date. Please request an over EES update for all facilities associated with this ANDA.

Bob

-----Original Message-----
From: Webber, Keith
Sent: Monday, February 07, 2011 8:55 AM
To: Friedman, Rick L
Cc: West, Robert L; Rickman, William P; Ames, Timothy W
Subject: RE: Change in classification

Thanks for the heads-up. Is the PAI going to happen before the status change or is the inspection just a routine biennial?

-----Original Message-----
From: Friedman, Rick L
Sent: Sunday, February 06, 2011 10:24 PM
To: Webber, Keith

Subject: Change in classification

Hi Keith-

Just a heads up that we are about to change Nostrum's compliance status to acceptable. We plan to do a PAI for certain pending manufacturing supplements/applications. Perhaps DMPQ and OGD should touch base to coordinate? For DMPQ, Tara would be the lead manager, as she is acting for Barry this week. Rick

Sent from BB. Please excuse typos.

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

/s/

STEVEN W YANG
02/07/2011

NOSTRUM
PHARMACEUTICALS, LLC

11D Jules Lane, New Brunswick, NJ 08901 Telephone: 732 543 2440 Fax: 732 246 7215

February 17, 2011

Keith Webber, Ph.D Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 7620
Standish Place
Rockville, Maryland 20855

MINOR AMENDMENT

- **cGMP Status Change Certification**
- **Chemistry Changes Updates**
- **Final Printed Labeling**

Re: ANDA 076-697 Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg

Dear Dr. Webber,

Pursuant to 21 CFR 314.60 (b)(3) on behalf of Nostrum Pharmaceuticals LLC ("NPLLC"), and Nostrum Laboratories Inc. ("NLI" and collectively " Nostrum"), the undersigned submits this Minor Amendment to the Abbreviated New Drug Application (ANDA) 076-697 for Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg (the "Product"), in response to the Agency's correspondence dated July 19, 2010 (Attachment 1).

Accordingly, Nostrum is submitting the following:

I. cGMP Status Change Certification:
As requested in the Agency's above mentioned correspondence, included in this submission is an updated cGMP certification from Nostrum's corporate officer representing the change of NLI's manufacturing facility's cGMP compliance status succeeding an inspection by the Kansas City District Office ("KANDO"). KANDO recently inspected NLI's facility (located at 1800 N Topping Ave, Kansas City, MO 64120. FEI 1930436) from October 13, 210 to November 5, 2010. Nostrum were informed on February 11, 2011 that as a result of this inspection the manufacturing site's cGMP status is being changes from "OAI" to "VAI". The statement from Nostrum's corporate officer is provided within Section 3.2.P.3.1.

II. Chemistry changes updates:
Reference is made to our teleconference with Mr. Robert West on February 14, 2011 in which the Agency requested that Nostrum provide all updated chemistry, manufacturing, and controls information with regard to the Product.

Minor changes have been made during the course of ongoing review for instructional clarification purposes, compliance with compendia, and other internal practices as NLI prepared

Following this page, 1 page withheld in full - (b)(4)

In addition, 36 month Room Temperature stability data for submission batches of all three strengths are being provided within Section 3.2.P.8.3. Accordingly, NLI proposes a (b) (4) (b) (4) expiration date for the Product at time of approval.

III. Final Printed Labeling

NLI's labeling has been revised to reflect the recent changes (effective Jan, 2011) to the Reference Listed Drug, Carbatrol®, which included addition of a Medication guide.

A summary of these changes and links for the labeling content are provided within Section 1.13.4.

We trust that this Minor Amendment satisfies all requirements for approval of this ANDA.

This submission is being filed electronically in eCTD format within sequence "0016" in the root folder "076697".

If you have any questions, please contact the undersigned at (732) 993-6210 or via facsimile at (816) 308-4975.

Sincerely,

Zoia Ploscaru

Digitally signed by Zoia Ploscaru
DN c US, st MO, l Kansas City, o Nostrum Laboratories, Inc., cn Zoia Ploscaru, email zploscaru@nostrumlabs.com
Date 2011.02.17 21 26 02 -05'00'

Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

CC: Robert L. West, Deputy Director, OGD
Vilayat Sayeed, Ph.D., Director, Division of Chemistry III

RECORD OF TELEPHONE CONVERSATION

Background Information:

Nostrum submitted AM on 2/17/11 to request full approval. The firm is requesting (b) (4) expiration date on the basis of 36 month data on submission batches. The firm can be granted 24 month of tentative expiration date.

Patankar called the firm on 2/23/11 at 11:00 am on Wednesday.

FDA:

The firm should submit an electronic amendment to acknowledge that the tentative expiration date of 2 years has been granted for the application.

Firm: The firm will submit an electronic amendment today.

DATE:
February 23, 2011

ANDA NUMBER:
076697

IND NUMBER:
N/A

TELECON

INITIATED BY:
APPLICANT
FDA

MADE:
BY TELEPHONE
IN PERSON

PRODUCT NAME:
Carbamazepine ER Capsules, 100 mg, 200 mg, 300 mg

FIRM NAME:
Nostrum Labs

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Zoia Polscaru, Reg. Affairs

TELEPHONE NUMBER:
732-993-6210

SIGNATURES:
Suhas Patankar

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

/s/

SUHAS J PATANKAR
02/23/2011

NOSTRUM
PHARMACEUTICALS, LLC

11D Jules Lane, New Brunswick, NJ 08901 Telephone: 732 543 2440 Fax: 732 246 7215

February 23, 2011

Keith Webber, Ph.D Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 7620
Standish Place
Rockville, Maryland 20855

TELEPHONE AMENDMENT

Re: ANDA 076-697 Carbamazepine Extended Release Capsules, 100 mg, 200 mg and 300 mg

Dear Dr. Webber,

Pursuant to 21 CFR 314.60 (b)(3) on behalf of Nostrum Pharmaceuticals LLC ("NPLLC"), and Nostrum Laboratories, Inc. ("NLI" and collectively " Nostrum"), the undersigned submits this Telephone Amendment to the Abbreviated New Drug Application (ANDA) 076-697 for Carbamazepine Extended Release Capsules, 100 mg, 200 mg and 300 mg (the "Product").

Reference is made to our teleconference with the Agency on February 23, 2011 where Nostrum was requested to address expiration date of 2 years for the product.

Nostrum acknowledges the tentative expiration date of 2 years has been granted for the product.

This submission is being filed electronically in eCTD format within sequence "0017" in the root folder "076697".

If you have any questions, please contact the undersigned at (732) 993-6210 or via facsimile at (816) 308-4975.

Sincerely,

Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

NOSTRUM
PHARMACEUTICALS, LLC

11D Jules Lane, New Brunswick, NJ 08901 Telephone: 732 543 2440 Fax: 732 246 7215

February 24, 2011

Keith Webber, Ph.D Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 7620
Standish Place
Rockville, Maryland 20855

LABELING AMENDMENT

Re: ANDA 076-697 Carbamazepine Extended-Release Capsules 100 mg, 200 mg and 300 mg

Dear Dr. Webber,

On behalf of Nostrum Pharmaceuticals LLC ("NPLLC"), and Nostrum Laboratories Inc. ("NLI" and collectively "Nostrum"), the undersigned submits this Labeling Amendment to the Abbreviated New Drug Application (ANDA) 076-697 for Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg.

Reference is made to the telephone conversation between the undersigned and the Agency on February 18, 2011 during which Nostrum was requested to submit the Risk Evaluation and Mitigation Strategy (REMS) to our labeling. Accordingly, Nostrum is submitting the REMS in Section 1.14.2.2.

This submission is being filed electronically in eCTD format within sequence "0018" in the root folder "076697". If you have any questions, please contact the undersigned at (732) 993-6210 or via facsimile at (816) 308-4975.

Sincerely,

Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com

NOSTRUM
PHARMACEUTICALS, LLC

11D Jules Lane, New Brunswick, NJ 08901 Telephone: 732 543 2440 Fax: 732 246 7215

March 10, 2011

Keith Webber, Ph.D Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 7620
Standish Place
Rockville, Maryland 20855

LABELING AMENDMENT

Re: ANDA 076-697 Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg

Dear Dr. Webber,

On behalf of Nostrum Pharmaceuticals LLC ("NPLLC"), and Nostrum Laboratories Inc. ("NLI" and collectively "Nostrum"), the undersigned submits this Labeling Amendment to the Abbreviated New Drug Application (ANDA) 076-697 for Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg.

Reference is also made to the email communication between the undersigned and the Agency on March 7, 2011 during which Nostrum was requested to revise the Description Section of the Prescribing Information (PI) and Medication Guide to correctly note all the inactive ingredients present including the imprint ink. Accordingly, Nostrum is submitting the following within **Section 1.14.2.2**:

1. Revised Package Insert and Medication guide for 300 mg
2. Revised Structured Product Labeling for 300 mg
3. Revised Side by Side Comparison with RLD for 300 mg
4. Revised Package insert and medication guide for 100 mg and 200 mg
5. Revised Structured Product Labeling for 100 mg and 200 mg
6. Revised Side by Side Comparison with RLD for 100 mg and 200 mg

If you have any questions, please contact the undersigned at (732) 993-6210 or via facsimile at (816) 308-4975.

Sincerely,

Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploacaru@nostrumlabs.com

NOSTRUM
PHARMACEUTICALS, LLC

11D Jules Lane, New Brunswick, NJ 08901 Telephone: 732 543 2440 Fax: 732 246 7215

March 15, 2011

Keith Webber, Ph.D Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 7620
Standish Place
Rockville, Maryland 20855

LABELING AMENDMENT

Re: ANDA 076-697 Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg

Dear Dr. Webber,

On behalf of Nostrum Pharmaceuticals LLC ("NPLLC"), and Nostrum Laboratories Inc. ("NLI" and collectively "Nostrum"), the undersigned submits this Labeling Amendment to the Abbreviated New Drug Application (ANDA) 076-697 for Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg.

Reference is made to recent communication between the undersigned and the Agency, during which Nostrum was requested to provide revised labeling, specifically, to include the inactive ingredients of the imprint ink.

Revised labeling to include ingredients of the imprint ink is being provided within Section 1.14.2 and supporting information from the imprint ink manufacturer is provided within Section 3.2.P.4.4:

1. Revised Package Insert and Medication guide for 300 mg
2. Revised Structured Product Labeling for 300 mg
3. Revised Side by Side Comparison with RLD for 300 mg
4. Revised Package Insert and Medication Guide for 100 mg and 200 mg
5. Revised Structured Product Labeling for 100 mg and 200 mg
6. Revised Side by Side Comparison with RLD for 100 mg and 200 mg

Please note certain inactive ingredient components which (b) (4)

All information has been provided in Sequence "0020" within the root folder "076697".

If you have any questions, please contact the undersigned at (732) 993-6210 or via facsimile at (816) 308-4975.

Sincerely,

Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploacaru@nostrumlabs.com

NOSTRUM
PHARMACEUTICALS, LLC

11D Jules Lane, New Brunswick, NJ 08901 Telephone: 732 543 2440 Fax: 732 246 7215

April 1, 2011

Keith Webber, Ph.D Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 7620
Standish Place
Rockville, Maryland 20855

LABELING AMENDMENT

Re: ANDA 076-697 Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg

Dear Dr. Webber,

On behalf of Nostrum Pharmaceuticals LLC ("NPLLC"), and Nostrum Laboratories Inc. ("NLI") and collectively ("Nostrum"), the undersigned submits this Labeling Amendment to the Abbreviated New Drug Application (ANDA) 076-697 for Carbamazepine Extended-Release Capsules, 100 mg, 200 mg and 300 mg.

Reference is made to recent communication between the undersigned and the Agency, during which Nostrum was requested to provide final printed medication guides.

The final printed medication guides including the side by side comparison is provided within Section 1.14.2:

1. Final Printed Medication guide for 300 mg
2. Revised Side by Side Medication Guide Comparison with RLD for 300 mg
3. Final Printed Medication Guide for 100 mg and 200 mg
4. Revised Side by Side Medication Guide Comparison with RLD for 100 mg and 200 mg

All information has been provided in Sequence "0021" within the root folder "076697".

If you have any questions, please contact the undersigned at (732) 993-6210 or via facsimile at (816) 308-4975.

Sincerely,

Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 33	PM: Bob Gaines

Electronic ANDA: Yes ☒ No ☐

ANDA #:076697
Firm Name:Nostrum Pharmaceuticals, LLC
ANDA Name:Carbamazepine Extended-release Capsules, 100 mg, 200 mg, and 300 mg
RLD Name:Carbatrol Capsules by Shrine

Electronic AP Routing Summary Located:
V:\Chemistry Division III\Team 33\Electronic AP Summary\76697.ap.doc

AP/TA Letter Located:
V:\Chemistry Division III\Team 33\PM Folder\Approval Letters\AP Letters\76697.apltr.DOC

Project Manager Evaluation: **Date: 2/23/11 Initials:** RG

☐ Previously reviewed and tentatively approved --- Date n/a
☒ Previously reviewed and CGMP Complete Response issued -- Date 7/19/10

Original Rec'd date 3/28/03	Date of Application 3/26/03	Date Acceptable for Filing 3/28/03
Patent Certification (type) P-IV	Date Patent/Excl. expires 7/15/16	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 4/18/11* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 2/24/11 Addendum Needed: Yes ☒ No ☐ Comment:
Date of Acceptable Bio 4/30/09 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 4/5/11 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☐; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☒ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 5/10/11 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☒

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☒ Division

☐ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Keith Webber

☐Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 5/17/2011**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =_____ NDA#_____
Patent/Exclusivity Certification: Yes ☒ No ☐	Date Checked _____
If Para. IV Certification- did applicant:	Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐	Written request issued ☐
Was applicant sued w/in 45 days:Yes ☒ No ☐	Study Submitted ☐
Has case been settled: Yes ☒ No ☐	
Date settled:	
Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐	
Date of latest Labeling Review/Approval Summary _____	

Any filing status changes requiring addition Labeling Review Yes ☐ No ☒

Type of Letter:

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP ☐ OTHER:

Comments:ANDA submitted on 3/28/2003, BOS=CARbatrol Capsules from Shire NDA 20-712, PIV to '013 and '570. RTR issued on 5/14/2003. ANDA ack for filing with PIV on 5/21/2003 on the 300 mg strength only (LO dated 6/23/2003). Patent amendment submitted on 8/12/2003-RR from Shire in Rockville MD signed and dated 8/4/2003. Patent Amendment submitted on 10/15/2003-CA # 03-4436(MLC) filed in the D of NJ on 9/18/2003 for infringement of the '570 and '013 patents. Missing 3.1 through 7.1 archival jackets. In the archival 9.1 jacket on 4/29/2008 the sponsor submitted an amendment for the 100 mg and 200 mg strengths, Same BOS as original, PIV to the '013 and '570 patents. Patent Amendment dated 7/24/2008-RR from Shire in Wayne Pa and Florence KY both signed with the Wayne PA receipt dated 5/19/2008-CA # 08-CV-03309-MLC-TJB filed in the D of NJ on 7/2/2008 for infringement of the '570 and '013 patents.

Firm needs to submit:
-status update for 03-4436
-status update for 08-03309

On 5/23/2009 the sponsor submitted a patent amendment through the gateway. The cover letter of this amendment indicates that both CA #s noted above remain pending with no decision rendered by the District Court. The 30 month stay of approval on the 300 mg strength expired long ago but the 30 month stay for the 100 mg and 200 mg strengths won't expire until 11/19/2010.

ANDA is eligible for split Full Approval on the 300 mg strength with 180 day exclusivity and Tentative Approval on the 100 mg and 200 mg strengths due to the unexpired 30 month stay of approval. The 180 day exclusivity for the 300 mg strength is governed by pre-MMA rules. Therefore, there will be no forfeiture of this exclusivity. It's noteworthy that the 180 day exclusivity for the 300 mg strength will be governed by pre-MMA rules whilst the 180 day exclusivity for the 100 mg and 200 mg will be governed by post-MMA rules. It appears but has not been confirmed that 180 day exclusivity has been forfeited for the 100 mg and 200 mg strengths. Whether the exclusivity for the 100 mg and 200 mg strengths has been forfeited does not need to be determined at this time as the Nostrum ANDA is only eligible for TA with respect to these strengths.

RSB contacted [redacted] (b) (4) TEVA (ANDA78-592) and Apotex (78-986) to ascertain whether any court had issued a decision which could be considered a trigger of Nostrum's 180 day exclusivity for the 300 mg strength. All cases remain pending with no decision or resolution.

Update 4/22/2010-the sponsor submitted a patent amendment which informed the Agency of two items. First- with respect to both CA 03-4436 and CA 08-3309, Nostrum and Shire entered into a consent agreement with judgment being issued by the court on 3/22/2010. Secondly, Nostrum has produced a letter on Shire letterhead which states that Shire and Nostrum have entered into a licensing agreement for both the '570 and '013 patent which will allow Nostrum to market on 10/1/2010. Shire also waived any interest in the maintenance of a 30 month stay. Shire also characterizes this settlement

as resolving the two NJ civil actions.
Applicant submitted a Patent Amendment on 6/21/2010-Letter from Nostrum in which they challenge the content of a letter from Apotex dated May 12, 2010 in which Apotex asserts that Nostrum is not eligible for 180 day exclusivity for the 300 mg strength of this drug product. Patent Amendment includes a letter on Shire letterhead in which Shire waives any interest in the maintenance of any 30 month stay.

[redacted] (b) (4)

pre-MMA trigger of 180 day exclusivity for Nostrum's ANDA. Therefore, any eligiblity for pre-MMA 180 day exclusivity that could be claimed by Nostrum was triggered in July of 2009 and has no expired. Nostrum remains eligible for 180 day exclusivity but solely with respect to the '570 patent which will expire on 7/5/2011. Nostrum's eligibility for 180 day exclusivity for the 300 mg strength will automatically truncate when the '570 patent expires.
ANDA is eligible for Full Approval for all three strengths [redacted] (b) (4)

(b) (4). Nostrum's approval letter should award them 180 day exclusivity solely with respect to the 300 mg strength.

2. ***Labeling Endorsement***

Reviewer, KS:
Date5/12/11
InitialsKS/RG for

Labeling Team Leader, LG:
Date5/12/11
InitialsLG/RG for

REMS required?
☒Yes ☐No

REMS acceptable?
☒Yes ☐No ☐n/a

Comments:
Thanks.

From: Golson, Lillie D
Sent: Thursday, May 12, 2011 2:44 PM
To: Gaines, Robert; Golson, Lillie D
Subject: FW: ANDA 76697 APPROVAL LABELING ENDORSEMENT

Hi Bob,

From a labeling standpoint, this application is acceptable for approval. please endorse the AP routing form on behalf of Kendra and me.

Thanks

Lillie

From: Gaines, Robert
Sent: Tuesday, May 10, 2011 1:52 PM
To: Stewart, Kendra; Golson, Lillie D
Subject: ANDA 76697 APPROVAL LABELING ENDORSEMENT

Good afternoon Kendra and Lillie.

ANDA 76697, Nostrum's Carbamazepine ER Capsules, is eligible for full approval of all strengths. Please provide the necessary labeling endorsement.

Thank you.

Bob

<< File: 76697.apltr.DOC >> << File: 76697 label rev.pdf >>

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 18May2011**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to the V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 5/18/11**
Chemistry Div. **III (Sayeed)** **InitialsVAS**
Comments:cmc satisfactory

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date_____**
Assoc. Dir. For Chemistry **Initials_____**
Comments: (First generic drug review)

OGD Office Management Evaluation

6. Peter Rickman **Date5/19/2011**
Director, DLPS **Initialswpr**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes ☐ No ☒
Petition: Yes☐ No☒
Comments:BOS=Carbatrol Capsules from Shire NDA 20-712, applicant provided PIV certs to '013 and '570 patents. Nostrum was sued for infringement of the '570 and '013 patents. The applicant submitted an amendment for the 100 mg and 200 mg strengths on 4/29/2008 (same BOS as original); Applicant provided PIV certs to the '013 and '570 patents. Nostrum was sued for infringement of the '570 and '013 patents. The 30 month stay of approval on all strengths has expired. Nostrum and Shire entered into a consent agreement with judgment being issued by the court on 3/22/2010. Nostrum has produced a letter on Shire letterhead which states that Shire and Nostrum have entered into a licensing agreement for both the '570 and '013 patent which will allow Nostrum to market on 10/1/2010, Shire also waived any interest in the maintenance of a 30 month stay. (b) (4) [redacted] a pre-MMA trigger of 180 day exclusivity for Nostrum's ANDA. Any eligiblity for pre-MMA 180 day exclusivity that could be claimed by Nostrum was triggered in July of 2009 and has now expired. Nostrum remains eligible for 180 day exclusivity but for the '570 patent which will expire on 7/5/2011. Nostrum's eligibility for 180 day exclusivity for the 300 mg strength will automatically truncate when the '570 patent expires. Labeling acceptable 4/5/2011 per AP Summary, TL sign-off 5/12/2011; Bio acceptable 4/30/2009; EER acceptable 4/18/2011.

ANDA is eligible for Full Approval for all three strengths. Nostrum's approval letter should award them 180 day exclusivity with respect to the 300 mg strength only.

AND/OR

7. Robert L. West **Date _____**
Deputy Director, OGD **Initials _____**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes☐ No☐
Petition: Yes☐ No☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments:

8. ***OGD Director Evaluation***
   Keith Webber
   Deputy Director, OPS
   Comments:
   First Generic Approval ☐
   PD or Clinical for BE ☐
   Special Scientific or Reg.Issue ☐
   Press Release Acceptable ☐

   Comments:

9. Project Manager
   Date 5/19/11
   Initials RG

   Check Communication and Routing Summary into DARRTS

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

/s/

ROBERT T GAINES
05/20/2011

NOSTRUM
PHARMACEUTICALS, LLC

11D Jules Lane, New Brunswick, NJ 08901 Telephone: 732 543 2440 Fax: 732 246 7215

May 20, 2011

Keith Webber, Ph.D. Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 7620
Standish Place
Rockville, Maryland 20855

NEW CORRESPONDENCE

Re: ANDA 076-697
Carbamazepine Extended Release Capsules, 100 mg, 200 mg and 300 mg

Dear Dr. Webber,

On behalf of Nostrum Pharmaceuticals LLC, and Nostrum Laboratories, Inc., collectively "Nostrum", the undersigned, submits this New Correspondence to inform the Agency that Nostrum is in receipt of the FDA's Final Approval Letter, dated May 20, 2011, for its Abbreviated New Drug Application 076697 Carbamazepine Extended Release Capsules, 100 mg, 200 mg and 300 mg.

With this correspondence, Nostrum notifies the Agency that it began commercial marketing of Carbamazepine Extended Release Capsules, 300 mg, on May 20, 2011.

Nostrum will comply with post-marketing requirements set forth in 21 CFR 314.80-81 and 314.98, and will advise the Office of Generic Drugs of any change in the marketing status of this product.

This submission is being filed electronically in eCTD format within sequence "0022" in the root folder "076697". Should you have any questions or require additional information, please contact the undersigned at (732) 993-6210 or via facsimile at (816) 308-4975.

Sincerely,

Zoia Ploscaru

Zoia Ploscaru
Regulatory Agent for NPLLC
Senior Director, Regulatory Affairs
Nostrum Laboratories, Inc.
1800 North Topping Avenue
Kansas City, MO 64120
zploscaru@nostrumlabs.com