

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-622/S-015

Name: Copaxane

Generic Name: glatiramer acetate for injection

Sponsor: Teva Neuroscience LLC

Approval Date: 07/12/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
NDA 20-622/S-015**

CONTENTS

Reviews / Information Included in this Review

Approval Letter	X
Approvable Letter(s)	X
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Administrative and Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-622/S-015

APPROVAL LETTER



NDA 20-622/S-015

TEVA Pharmaceuticals USA
Attention: Dr. J. Michael Nicholas
Senior Director, Regulatory Affairs
1090 Horsham Road
North Wales, PA 19454

Dear Dr. Nicholas:

Please refer to your supplemental new drug application dated March 16, 2001, received March 19, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Copaxone (glatiramer acetate) for Injection 20mg/vial.

We acknowledge receipt of your submission dated March 16, 2001. Your submission of March 16, 2001 constituted a complete response to our January 19, 2001 action letter.

This supplemental new drug application proposes numerous changes to the Copaxone Injection product labeling.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling text agreed to in our facsimile of June 29, 2001. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling faxed on June 29, 2001 and which is appended to this letter. These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-622/S-015/S-015." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

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

/s/

Russell Katz
7/12/01 08:55:05 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-622/S-015

APPROVABLE LETTER(S)



NDA 20-622/S-015

TEVA Pharmaceuticals, USA
Attention: Scott L. Grossman, Ph.D.
Director, Regulatory Affairs
1090 Horsham Road
North Wales, PA 19454

Dear Dr. Grossman:

Please refer to your supplemental new drug application S-015 dated August 4, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Copaxone (glatiramer acetate) for Injection 20mg/vial.

We acknowledge receipt of your submissions dated:

April 20, 2000	October 11, 2000	October 16, 2000
November 14, 2000	November 21, 2000	January 5, 2001

This supplemental new drug application proposes for the use of Copaxone Injection for the management of relapsing-remitting multiple sclerosis by reducing the frequency of relapses []

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Although we consider the application Approvable, we have extensive revisions to the labeling you have proposed, the more important of which are described below. In addition, we have several critical questions about the nature of the informed consent obtained in Study 9003 which must be satisfactorily answered before the application may be approved.

Study 9003

As you know, we have residual, serious concerns about the nature of the informed consent process utilized in this study. It is critical that these concerns be addressed. In the absence of adequate responses to these questions, we might conclude that the trial did not meet current ethical guidelines and regulations, and the results may not be acceptable for inclusion in labeling.

Specifically, we would like you to submit a detailed description of the events surrounding the efforts to re-obtain informed consent from those patients already

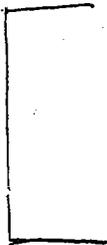
enrolled in the Canadian study at the time that Copaxone became available in Canada. Please include a description of the nature of the revised consent (if any) obtained (e.g., written or oral, and, if oral, the content of the information given to patients), and detailed documentation of how such revised consent was obtained.

In addition, we acknowledge that Dr. Rice did not obtain proper written informed consent from his patients reflecting that Copaxone became available in Canada, but that he states that he did inform his patients orally of its availability. We are unclear about whether or not this applied only to patients newly enrolled from that time forward, or whether he also informed patients already enrolled at his site of Copaxone's availability. Please clarify this point, and please tell us the details of the information Dr. Rice gave to his patients. In particular, it will be critical to know whether Dr. Rice simply informed his patients of Copaxone's availability, or if he explicitly obtained (oral) consent from them to continue in the trial.

Also, we request that you submit a detailed account of the decision to continue the study after the results of the second interim analysis were found to meet the protocol stopping rule. This description should include the reasons for this decision, and any contemporaneous documentation of discussions held on this matter (e.g., minutes of the meeting of the Executive Committee during which we are given to understand the decision was made).

Labeling

As discussed in our meeting of January 11, 2001, we have concluded that most of the changes you have proposed for the Clinical Trials sub-section of the Clinical Pharmacology section of labeling are unacceptable.



We are willing to include a description of the primary result of Study 9003 in labeling, because we believe that it provides useful information to the prescriber.





In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide an electronic and highlighted or marked-up copy that shows the changes that are being made. For ease of review, we have made changes to your proposed labeling dated November 14, 2000.

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

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-622/S-015

FINAL PRINTED LABELING

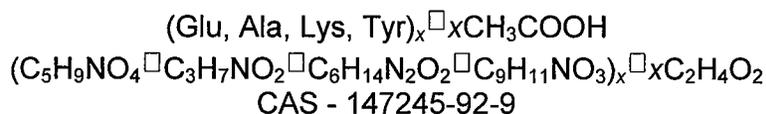
COPAXONE®

(glatiramer acetate for injection)

DESCRIPTION

COPAXONE® is the brand name for glatiramer acetate (formerly known as copolymer-1). Glatiramer acetate, the active ingredient of COPAXONE®, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 4,700–11,000 daltons.

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:



COPAXONE® is a white to off-white, sterile, lyophilized powder containing 20 mg of glatiramer acetate and 40 mg of mannitol. It is supplied in single-use vials for subcutaneous administration after reconstitution with the diluent supplied (Sterile Water for Injection).

CLINICAL PHARMACOLOGY**Mechanism of Action**

The mechanism(s) by which glatiramer acetate exerts its effects in patients with Multiple Sclerosis (MS) is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in several animal species through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and *in vitro* systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery.

Because glatiramer acetate can modify immune functions, concerns exist about its potential to alter naturally occurring immune responses. Results of a limited battery of tests designed to evaluate this risk produced no finding of concern; nevertheless, there is no logical way to absolutely exclude this possibility (see **PRECAUTIONS**).

Pharmacokinetics

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support the assumption that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Nevertheless, larger fragments of glatiramer acetate can be recognized by glatiramer acetate-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

Clinical Trials

Evidence supporting the effectiveness of glatiramer acetate in decreasing the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RR MS) derives from two placebo-controlled trials, both of which used a glatiramer acetate dose of 20 mg/day. (No other dose or dosing regimen has been studied in placebo-controlled trials of RR MS.)

One trial was performed at a single center. It enrolled 50 patients who were randomized to receive daily doses of either glatiramer acetate, 20 mg subcutaneously, or placebo (glatiramer acetate, n=25; placebo, n=25). Patients were diagnosed with RR MS by standard criteria, and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale ranging from 0–Normal to 10–Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.

Patients were examined every 3 months for 2 years, as well as within several days of a presumed exacerbation. To confirm an exacerbation, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the neurological signs for at least 48 hours).

The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but two other important outcomes were also specified as endpoints: 1) the frequency of attacks during the trial, and 2) the change in the number of attacks compared with the number which occurred during the previous 2 years.

Table 1 presents the values of the three outcomes described above, as well as several protocol specified secondary measures. These values are based on the intent-to-treat population (i.e., all patients who received at least 1 dose of treatment and who had at least 1 on-treatment assessment):

Table 1: Study 1 Efficacy Results

Outcome	Glatiramer Acetate (N=25)	Placebo (N=25)	P-Value
% Relapse Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate Compared to Pre-	3.2	1.6	0.025

Study			
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

*Progression was defined as an increase of at least 1 point on the DSS, persisting for at least 3 consecutive months.

The second trial was a multicenter trial of similar design which was performed in 11 US centers. A total of 251 patients (glatiramer acetate, 125; placebo, 126) were enrolled. The primary outcome measure was the Mean 2-year Relapse Rate. The table below presents the values of this outcome for the intent-to-treat population, as well as several secondary measures.

Table 2: Study 2 Efficacy Results

Outcome	Glatiramer Acetate (N=125)	Placebo (N=126)	P-Value
Mean No. of Relapses	1.19/2 years	1.68 /2 years	0.055
% Relapse Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Patients Progression Free	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05	+0.21	0.023

In both studies glatiramer acetate exhibited a clear beneficial effect on relapse rate, and it is based on this evidence that glatiramer acetate is considered effective.

A third study was a multi-national study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RR MS (119 on glatiramer acetate and 120 on placebo) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the nine months. Table 3 summarizes the result for the primary outcome measures monitored during the trial for the intent-to-treat cohort.

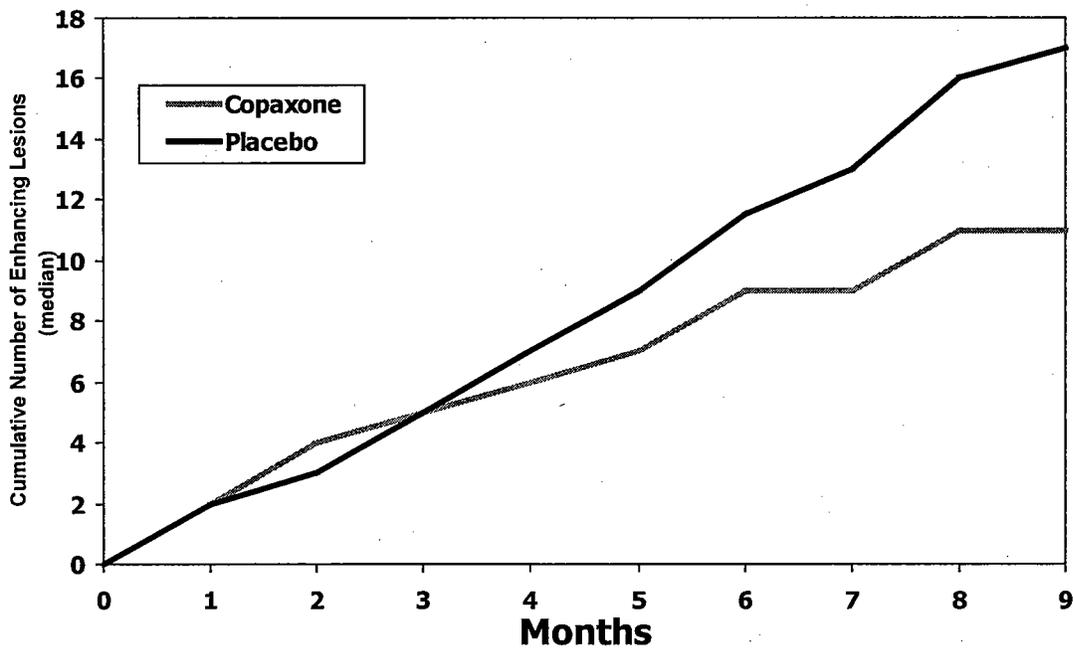
Table 3: Study 3 MRI Results

Outcome	Glatiramer	Placebo	p-value
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	Acetate (N=119)	(N=120)	
Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	11	17	0.0030

The following figure displays the results of the primary outcome on a monthly basis.

Figure 1: Median Cumulative Number of Gd-Enhancing Lesions



p= 0.003 for the difference between the placebo-treated (n=120) and glatiramer acetate-treated (n=119) groups.

INDICATIONS AND USAGE

COPAXONE® is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis.

CONTRAINDICATIONS

COPAXONE® is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

WARNINGS

The only recommended route of administration of COPAXONE® injection is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

PRECAUTIONS

General

Patients should be instructed in self-injection techniques to assure the safe administration of COPAXONE® (see **PRECAUTIONS: Information for Patients** and the **COPAXONE® PATIENT INFORMATION** Booklet). Current data indicate that no special caution is required for patients operating an automobile or using complex machinery.

Considerations Regarding the Use of a Product Capable of Modifying Immune Responses

Because glatiramer acetate can modify immune response, it could possibly interfere with useful immune functions. For example, treatment with glatiramer acetate might, in theory, interfere with the recognition of foreign antigens in a way that would undermine the body's tumor surveillance and its defenses against infection. There is no evidence that glatiramer acetate does this, but there has as yet been no systematic evaluation of this risk. Because glatiramer acetate is an antigenic material it is possible that its use may lead to the induction of host responses that are untoward, but systematic surveillance for these effects has not been undertaken.

Although glatiramer acetate is intended to minimize the autoimmune response to myelin, there is the possibility that continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RR MS patients given glatiramer acetate, 20 mg, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded.

Information for Patients

To assure safe and effective use of COPAXONE®, the following information and instructions should be given to patients:

1. Inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while taking this medication.
2. Inform your physician if you are nursing.
3. Do not change the dose or dosing schedule without consulting your physician.
4. Do not stop taking the drug without consulting your physician.

Patients should be instructed in the use of aseptic techniques when administering COPAXONE®. Appropriate instructions for the reconstitution and self-injection of COPAXONE® should be given, including a careful review of the **COPAXONE® PATIENT INFORMATION** Booklet. The first injection should be performed under the supervision of an appropriately qualified health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically reevaluated. Patients should be cautioned against the reuse of needles or syringes and instructed in safe disposal procedures. They should use a puncture-resistant container for disposal of used needles and syringes. Patients should be instructed on the safe disposal of full containers according to local laws.

Awareness of Adverse Reactions: Physicians are advised to counsel patients about adverse reactions associated with the use of COPAXONE® (see **ADVERSE REACTIONS** section). In addition, patients should be advised to read the **COPAXONE® PATIENT INFORMATION** Booklet and resolve any questions regarding it prior to beginning COPAXONE® therapy.

Laboratory Tests

Data collected during premarketing development do not suggest the need for routine laboratory monitoring.

Drug Interactions

Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta.

Drug/Laboratory Test Interactions

None are known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a two-year carcinogenicity study, mice were administered up to 60-mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m² basis). No increase in systemic neoplasms was observed. In males of the high dose group (60 mg/kg/day), but not in females, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a two-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m² basis). No increase in systemic neoplasms was observed.

Mutagenesis

Glatiramer acetate was not mutagenic in four strains of *Salmonella typhimurium* and two strains of *Escherichia coli* (Ames test) or in the *in vitro* mouse lymphoma assay in L5178Y cells. Glatiramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes; it was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

In a multigeneration reproduction and fertility study in rats, glatiramer acetate at subcutaneous doses of up to 36 mg/kg (18 times the human therapeutic dose on a mg/m² basis) had no adverse effects on reproductive parameters.

Pregnancy: Pregnancy Category B. No adverse effects on embryofetal development occurred in Reproduction studies in rats and rabbits receiving subcutaneous doses of up to 37.5 mg/kg of glatiramer acetate during the period of organogenesis (18 and 36 times the therapeutic human dose on a mg/m² basis respectively). In a prenatal and postnatal study in which rats received subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, glatiramer acetate should be used during pregnancy only if clearly needed.

Labor and Delivery

In a prenatal and postnatal study, in which rats received subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery were observed. The relevance of these findings to humans is unknown.

Nursing Mothers

It is not known whether glatiramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COPAXONE® is administered to a nursing woman.

Pediatric Use

The safety and efficacy of COPAXONE® have not been established in individuals under 18 years of age.

Use in the Elderly

COPAXONE® has not been studied specifically in elderly patients.

Use in Patients with Impaired Renal Function

The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not

been determined.

ADVERSE REACTIONS

During premarketing clinical trials approximately 900 individuals received at least one dose of glatiramer acetate.

In controlled clinical trials the most commonly observed adverse experiences associated with the use of glatiramer acetate and not seen at an equivalent frequency among placebo-treated patients were: injection site reactions, vasodilatation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety, and hypertonia.

Approximately 8% of the 893 subjects receiving glatiramer acetate discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilatation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness, and tremor.

Immediate Post-Injection Reaction

Approximately 10% of MS patients exposed to glatiramer acetate in premarketing studies experienced a constellation of symptoms immediately after injection that included flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. In clinical trials, the symptoms were generally transient and self-limited and did not require specific treatment. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care.

Whether an immunologic or non-immunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

Chest Pain

Approximately 21% of glatiramer acetate patients in the pre-marketing controlled studies (compared to 11% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of this chest pain to an injection of glatiramer acetate was not always known. The pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. There has been only one episode of chest pain during which a full EKG was performed; that EKG showed no evidence of ischemia. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.

Incidence in Controlled Clinical Studies: The following table lists treatment-emergent signs

and symptoms that occurred in at least 2% of MS patients treated with glatiramer acetate in the pre-marketing placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with glatiramer acetate than in patients treated with placebo. These trials include the first two controlled trials in RR MS patients and a controlled trial in patients with Chronic-Progressive MS. Adverse reactions were usually mild in intensity.

The prescriber should be aware that these figures cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis on which to estimate the relative contribution of drug and nondrug factors to the adverse reaction incidences in the population studied.

**Controlled Trials in Patients with Multiple Sclerosis:
Incidence of Glatiramer Acetate Adverse Reactions \geq 2%
and More Frequent than Placebo**

Preferred Term	<u>Glatiramer Acetate</u> (N = 201)		<u>Placebo</u> (N = 206)	
	N	%	N	%
Body as a Whole				
Asthenia	83	41	78	38
Back Pain	33	16	30	15
Bacterial Infection	11	5	9	4
Chest Pain	43	21	22	11
Chills	8	4	2	1
Cyst	5	2	1	0
Face Edema	12	6	2	1
Fever	17	8	15	7
Flu Syndrome	38	19	35	17
Infection	101	50	99	48
Injection Site Erythema	132	66	40	19
Injection Site Hemorrhage	11	5	6	3
Injection Site Induration	26	13	1	0

Preferred Term	Glatiramer Acetate (N = 201)		Placebo (N = 206)	
	N	%	N	%
Injection Site Inflammation	98	49	22	11
Injection Site Mass	54	27	21	10
Injection Site Pain	147	73	78	38
Injection Site Pruritus	80	40	12	6
Injection Site Urticaria	10	5	0	0
Injection Site Welt	22	11	5	2
Neck Pain	16	8	9	4
Pain	56	28	52	25
Cardiovascular System				
Migraine	10	5	5	2
Palpitations	35	17	16	8
Syncope	10	5	5	2
Tachycardia	11	5	8	4
Vasodilatation	55	27	21	10
Digestive System				
Anorexia	17	8	15	7
Diarrhea	25	12	23	11
Gastroenteritis	6	3	2	1
Gastrointestinal Disorder	10	5	8	4
Nausea	44	22	34	17
Vomiting	13	6	8	4
Hemic and Lymphatic System				
Ecchymosis	16	8	13	6

Preferred Term	<u>Glatiramer Acetate</u> (N = 201)		<u>Placebo</u> (N = 206)	
	N	%	N	%
Lymphadenopathy	25	12	12	6
Metabolic and Nutritional				
Edema	5	3	1	0
Peripheral Edema	14	7	8	4
Weight Gain	7	3	0	0
Musculoskeletal System				
Arthralgia	49	24	39	19
Nervous System				
Agitation	8	4	4	2
Anxiety	46	23	40	19
Confusion	5	2	1	0
Foot Drop	6	3	4	2
Hypertonia	44	22	37	18
Nervousness	4	2	2	1
Nystagmus	5	2	2	1
Speech Disorder	5	2	3	1
Tremor	14	7	7	3
Vertigo	12	6	11	5
Respiratory System				
Bronchitis	18	9	12	6
Dyspnea	38	19	15	7
Laryngismus	10	5	7	3
Rhinitis	29	14	27	13

Preferred Term	<u>Glatiramer Acetate</u> (N = 201)		<u>Placebo</u> (N = 206)	
	N	%	N	%
Skin and Appendages				
Erythema	8	4	4	2
Herpes Simplex	8	4	6	3
Pruritus	36	18	26	13
Rash	37	18	30	15
Skin Nodule	4	2	1	0
Sweating	31	15	21	10
Urticaria	9	4	5	2
Special Senses				
Ear Pain	15	7	12	6
Eye Disorder	8	4	1	0
Urogenital System				
Dysmenorrhea	12	6	10	5
Urinary Urgency	20	10	17	8
Vaginal Moniliasis	16	8	9	4

Other events which occurred in at least 2% of glatiramer acetate patients but were present at equal or greater rates in the placebo group included:

Body as a Whole: Headache, injection site ecchymosis, accidental injury, abdominal pain, allergic rhinitis, neck rigidity, and malaise.

Digestive System: Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth.

Musculoskeletal: Myasthenia and myalgia.

Nervous System: Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign,

abnormal thinking, twitching, euphoria, and sleep disorder.

Respiratory System: Pharyngitis, sinusitis, increased cough and laryngitis.

Skin and Appendages: Acne, alopecia, and nail disorder.

Special Senses: Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness.

Urogenital System: Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse reactions occurring in the controlled clinical trials were analyzed to evaluate differences based on sex. No clinically significant differences were identified. Ninety-two percent of patients in these clinical trials were Caucasian. This percentage reflects the racial composition of the MS population. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for glatiramer acetate. Clinically significant laboratory values for hematology, chemistry, and urinalysis were similar for both glatiramer acetate and placebo groups in blinded clinical trials. No patient receiving glatiramer acetate withdrew from any trial because of abnormal laboratory findings.

Other Adverse Events Observed During Clinical Trials

Glatiramer acetate was administered to 979 individuals during premarketing clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators, using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into standardized categories using COSTART dictionary terminology. All reported events occurring at least twice and potentially important events occurring once are listed below, except those already listed in the previous table, those too general to be informative, trivial events, and other reactions which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group. Additional adverse reactions reported during the post-marketing period are included.

Events are further classified within body system categories and listed in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *Rare* adverse events are those occurring in less than 1/1000 patients.

Body as a Whole:

- ◆ *Frequent:* Injection site edema, injection site atrophy, abscess, injection site hypersensitivity.
- ◆ *Infrequent:* Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.

Cardiovascular:

- ◆ *Frequent:* Hypertension.
- ◆ *Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive:

- ◆ *Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration, and duodenal ulcer.

Endocrine:

- ◆ *Infrequent:* Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal:

- ◆ *Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.

Hemic and Lymphatic:

- ◆ *Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

Metabolic and Nutritional:

- ◆ *Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal:

- ◆ *Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

Nervous:

- ◆ *Frequent:* Abnormal dreams, emotional lability, and stupor.
- ◆ *Infrequent:* Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:

- ◆ *Frequent:* Hyperventilation, hay-fever.
- ◆ *Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages:

- ◆ *Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy, and warts.
- ◆ *Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous

rash.

Special Senses:

- ◆ *Frequent:* Visual field defect.
- ◆ *Infrequent:* Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital:

- ◆ *Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious papanicolaou smear, urinary frequency and vaginal hemorrhage.
- ◆ *Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Postmarketing Clinical Experience

Postmarketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE ®(glatiramer acetate) not mentioned above that have been received since market introduction and that may have or not have causal relationship to the drug include the following:

Body as a Whole: sepsis; LE syndrome; hydrocephalus; enlarged abdomen; injection site hypersensitivity; allergic reaction; anaphylactoid reaction

Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy cardiomegaly; arrhythmia; angina pectoris

Digestive System: tongue edema; stomach ulcer hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasia; convulsion; neuralgia

Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung; hay fever

Special Senses: glaucoma; blindness; visual field defect

Urogenital System: urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

DRUG ABUSE AND DEPENDENCE

No evidence or experience suggests that abuse or dependence occurs with COPAXONE® therapy; however, the risk of dependence has not been systematically evaluated.

DOSAGE AND ADMINISTRATION

The recommended dose of COPAXONE® for the treatment of RR MS is 20 mg/day injected subcutaneously.

Instructions for Use

To reconstitute lyophilized COPAXONE® for injection, use a sterile syringe and Mixject Vial Adapter to transfer the diluent supplied, Sterile Water for Injection, into the COPAXONE® vial. Gently swirl the vial of COPAXONE® and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist before use if it contains particulate matter.

Soon after reconstitution, withdraw the solution into the syringe. Replace the Mixject Vial Adapter with a 27 gauge, ½" needle and inject the solution subcutaneously. Sites for self-injection include arms, abdomen, hips, and thighs. A vial is suitable for single use only; unused portions should be discarded. (See the **COPAXONE® PATIENT INFORMATION** Booklet for **INSTRUCTIONS FOR INJECTING COPAXONE®**.)

HOW SUPPLIED

COPAXONE® is supplied as a sterile, lyophilized material containing 20 mg of glatiramer acetate and 40 mg of mannitol, USP. The drug is packaged in a USP Type 1 amber glass, single-use 2 mL vial. A separate vial, containing 1.1 mL of diluent (Sterile Water for Injection) is included for each vial of drug.

The recommended storage condition for the unreconstituted product is refrigeration (2°C to 8°C / 36°F to 46°F). However, excursions from recommended storage conditions to room temperature conditions (15° to 30°C / 59° to 86° F) for up to one week have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided.

The diluent may be stored at room temperature.

COPAXONE® contains no preservative. It should be used immediately after reconstitution.

COPAXONE® is available in packs of 32 amber vials of sterile, lyophilized material for subcutaneous injection (NDC 0088-1150-03). The diluent for COPAXONE® is supplied in packs of 32 clear vials.

Rx only.

COPAXONE® (glatiramer acetate for injection)

PATIENT INFORMATION

This booklet tells patients about COPAXONE® [coe PAX own] (glatiramer acetate for injection, formerly known as copolymer-1) and how to use COPAXONE® with the Mixject Vial Adapter. COPAXONE® treats Relapsing-Remitting Multiple Sclerosis.

- ▲ Before you begin using COPAXONE®, make sure you understand all the information in this booklet about its possible benefits and risks. If you do not understand some of the information in this booklet, contact your doctor for help.
- ▲ COPAXONE® is not recommended for use in pregnancy. Therefore, tell your doctor if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medicine.
- ▲ Tell your doctor if you are nursing. We do not know if COPAXONE® is passed through the milk to the baby.
- ▲ Do not change the dose or dosing schedule without talking with your doctor.
- ▲ Do not stop taking the drug without talking with your doctor.
- ▲ The most common side effects of COPAXONE® are redness, pain, swelling, itching, or a lump at the site of injection. These reactions are usually mild and seldom require professional treatment. Be sure to tell your doctor about any side effects.
- ▲ Some patients report a short-term reaction right after injecting COPAXONE®. This reaction can involve flushing (feeling of warmth and/or redness), chest tightness or pain with heart palpitations, anxiety, and trouble breathing. These symptoms generally appear within minutes of an injection, last about 15 minutes, and go away by themselves without further problems.
- ▲ After you inject COPAXONE®, call your doctor right away if you develop hives, skin rash with irritation, dizziness, sweating, chest pain, trouble breathing, severe pain at the injection site or other uncomfortable changes in your general health. Make no more injections until your doctor tells you to begin again.
- ▲ If symptoms become severe, call the appropriate emergency phone number in your area. Make no more injections until your physician tells you to begin again.
- ▲ Your prescription includes two types of vials (small bottles): brown vials containing COPAXONE® and clear vials of sterile water (diluent).
- ▲ Store the brown vials of COPAXONE® in the refrigerator as soon as you bring them home.
- ▲ Store the clear vials labeled “Sterile Water for Injection” (diluent) at room temperature.

- ▲ Keep COPAXONE® out of the reach of children.

INSTRUCTIONS FOR MIXING (RECONSTITUTING) AND INJECTING COPAXONE®

Read all of the following instructions before you reconstitute and inject COPAXONE®.

Are you left-handed?

Drawings in this leaflet show patients who are right-handed. If you are left-handed, do what comes naturally. You will probably find it most comfortable to hold the syringe in your left hand, and hold the vial between thumb and forefinger of your right hand.

Safety Tips:

- Use only the supplies provided with your COPAXONE® kit.
- Wash your hands well before beginning. Do not touch your hair or skin after washing.
- Keep the items sterile. Do not touch the needle, the piercing spike of the vial adapter, or the tops of the cleaned vials.
- Make sure none of the items in your kit have been opened.
- Never mix COPAXONE® with tap water.
- Do not reuse opened materials. Throw away unused portions of the COPAXONE® and sterile water (diluent).
- Throw away used syringes in a proper container. Ask your doctor if you do not know how to do this.
- Contact your doctor if you have questions.

There are 4 basic steps for injecting COPAXONE®:

1. Gathering the materials.
2. Mixing COPAXONE® and sterile water (reconstitution). This involves adding sterile water to the dry COPAXONE®.
3. Preparing the injection syringe.
4. Giving yourself the injection.

STEP 1. Gathering the Materials

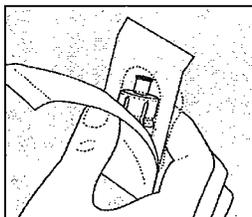
- 1) Put the items you will need on a clean flat surface in a well-lighted area. The items and where you will find them are listed in the table below.

The item	Supplied in
• 1 brown vial of COPAXONE®	COPAXONE® drug product package

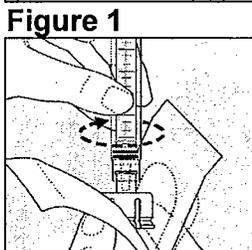
<ul style="list-style-type: none"> • 1 clear vial of Sterile Water For Injection, USP (diluent) • 1 syringe (3cc)* • 1 injection needle (27 gauge, ½") • 1 Mixject Vial Adapter • 3 alcohol wipes (preps or swabs) 	<p>Self Injection Administration Package</p>
<ul style="list-style-type: none"> • 1 Dry cotton ball 	<p>Not supplied</p>

*One cubic centimeter (cc) represents the same amount as one-milliliter (mL). Use the scale that is on the syringe.

- 2) To prevent infection, wash and dry your hands. Do not touch your hair or skin after washing.
- 3) Remove the 3-cc syringe from its protective wrapper by peeling back the paper label.
- 4) Place the syringe on the clean surface.
- 5) Remove the injection needle from its protective wrapper by peeling back the paper label. Place the injection needle on the clean surface. Do not remove the plastic needle shield yet.



6) Open the Mixject Vial Adapter package by peeling back the paper and the plastic. Peel back only half-way. Do not open the package completely. Hold the wide side of the Mixject Vial Adapter through the package so you will not get germs on the Mixject Vial Adapter (Figure 1).



7) Remove the plastic tip cap from the 3-cc syringe. Without removing the Mixject Vial Adapter from its package, connect the syringe to the Mixject Vial Adapter by twisting the syringe (rotation). Make sure that the syringe is tightly attached to the Mixject Vial Adapter (Figure 2).

Figure 2

- 8) Place the package containing the Mixject Vial Adapter with the attached syringe on the clean surface.
- 9) Remove the plastic cover from the clear sterile water (diluent) vial. Use an alcohol wipe to clean the rubber top. Do the same for the brown COPAXONE® vial with a fresh alcohol wipe. **Do not touch the rubber tops after they are cleaned.** Let both rubber tops dry for a few seconds.

Important:

- To avoid spreading germs, do not touch any of the following:

the needle
 the piercing spike of the Mixject Vial Adapter
 the top of either vial

- Use only the Sterile Water for Injection, USP (diluent) from the Self Injection Administration Package when mixing (reconstituting) COPAXONE®.
- If you have questions, contact your doctor or nurse before going further in reconstituting and injecting COPAXONE®. You may also contact **Shared Solutions™** by calling 1-800-887-8100.

STEP 2. Mixing COPAXONE® and Diluent (Reconstitution)

1) Hold the syringe with one hand. Remove the Mixject Vial Adapter from its paper wrapper. Do not touch the Mixject Vial Adapter. Pull the plunger back to the 1.1 cc line to draw air into the syringe (see insert, Figure 5).

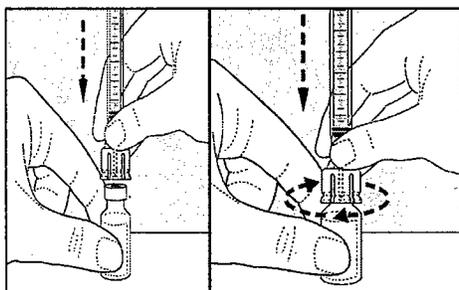


Figure 3

2) With 2 fingers of one hand, hold the clear diluent vial on a stable surface like a table or kitchen counter. Hold the connection between the Mixject Vial Adapter and the syringe with the other hand. Insert the piercing spike of the Mixject Vial Adapter all the way in through the rubber top of the clear sterile water vial, using a rotating and pushing movement. (Figure 3)

3) Push the plunger of the syringe all the way in.

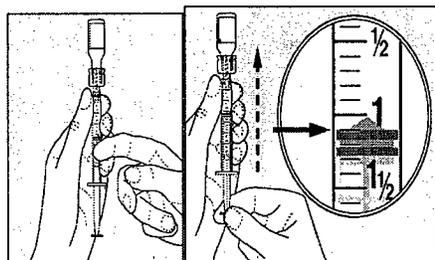


Figure 4

Figure 5

4) Turn the connected syringe and vial upside down and pull the plunger out until all the diluent is drawn into the syringe. If there are air bubbles inside the syringe, tap the side of the syringe to make them float to the top (Figure 4). Push the plunger in until the top of the black plunger ring is in line with the bottom of the 1.1 cc line on the syringe (as shown by the arrow in Figure 5).

5) Holding the syringe containing the sterile water (diluent) and the Mixject Vial Adapter, remove the clear vial. Throw it away by putting it in a safe hard-walled container, such as an empty liquid laundry detergent container.

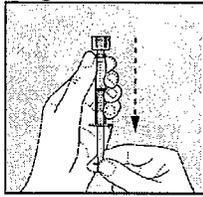


Figure 6

6) Take the 3 cc syringe containing the sterile water (diluent) and pull the plunger back to the 2.0 cc line to draw air into the syringe (Figure 6).

7) Hold the brown COPAXONE® vial on a stable surface with 2 fingers of one hand. Hold the connected Mixject Vial Adapter and the syringe with the other hand. Insert the piercing spike of the Mixject Vial Adapter all the way in through the rubber top of the COPAXONE® vial, using a rotating and pushing movement.

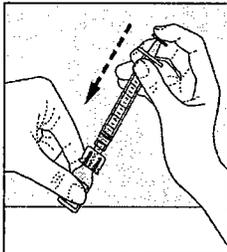


Figure 7

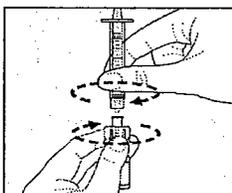
8) Slowly inject all the sterile water and air into the vial by pressing the plunger all the way in. To avoid bubbles, do not inject the sterile water directly onto the COPAXONE®. Instead, inject the sterile water so it runs down the inside of the vial glass. You can do this if you keep the vial tilted while injecting (Figure 7).

9) **Do not shake the vial.** Gently swirl the COPAXONE® vial until all the medicine dissolves and the solution looks clear. The COPAXONE® is now mixed (reconstituted). Keeping the vial, adapter, and syringe connected, leave the vial at room temperature for about 5 minutes.

10) Look for particles in the solution. Do not use the solution if there are any particles in it.

STEP 3: Preparing the Injection Syringe

1) Hold the syringe with one hand and make sure that the plunger is pressed all the way in. Turn the vial upside down. To give the full dose of COPAXONE®, withdraw all of the solution into the syringe and Mixject Vial Adapter by slowly pulling the plunger out. This amount will be about 1.1 cc. Again, if there are air bubbles inside the syringe, tap the side of the syringe to make them float to the top. Inject any air back into the vial by pushing the plunger in gently.



2) Keep the brown vial of COPAXONE® and the Mixject Vial Adapter connected to each other. Disconnect them from the syringe by turning them together (rotation) (Figure 8). Throw away the COPAXONE® vial and the Mixject Vial Adapter by putting them in a safe hard-walled container.

Figure 8

- 3) When you connect the injection needle (27 gauge, ½") to the syringe, keep the plastic cover on the needle. Make sure that the needle is tightly placed in its proper position. The syringe is now ready to use.
- 4) Place the ready-to-use syringe on the clean surface.

STEP 4: Giving Yourself the Injection

Before you begin the procedure to self-inject the COPAXONE®:

- ▲ **Decide where you will inject yourself.** There are seven injection sites on your body, and **you should not use any site more than once each week.** Marking a calendar each day will help you keep track of the sites you have used (Figure 9).
- ▲ **Be consistent.** Give yourself the injection at the same time each day. Choose a time when you feel strongest.
- ▲ **Have a friend or relative with you if you need help.** You may have had a friend attend the injection training session as your assistant. Especially when you first start giving yourself injections, your assistant should be with you.

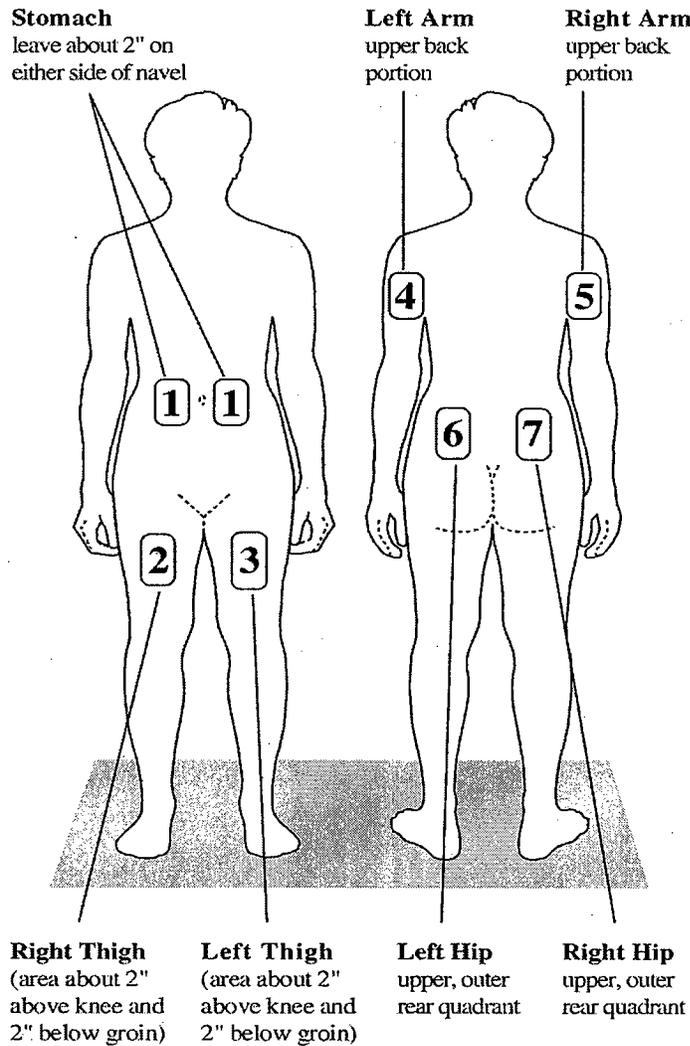


Figure 9

- 1) Clean the injection site with a fresh alcohol wipe. Let the site dry.
- 2) Pick up the 3-cc syringe you already filled with COPAXONE® as you would pick up a pencil, using the hand you write with. Remove the plastic cover from the needle.

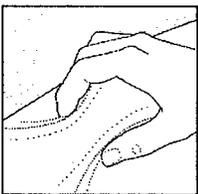


Figure 10

- 3) For sites that are **not** on the back of your arms, pinch about a 2-inch fold of skin between your thumb and index finger of your other hand. (Figure 10).

- 4) Holding the syringe straight up and down insert the needle into the 2-inch fold of skin. It may help to steady your hand by resting the heel of your hand against your body.

How do I reach the upper back of my arms?

For the 2 injection sites on the upper back of the arms, it is not possible to pinch 2 inches of skin with one hand and inject yourself with the other hand. Ask your nurse for instructions on how to use these sites.

- 5) When the needle is all the way in, release the fold of skin.
- 6) Inject the medicine by holding the syringe steady while pushing down on the plunger. The injection should take just a few seconds (Figure 11).

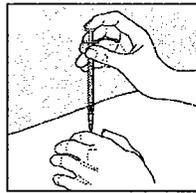


Figure 11

- 7) Pull the needle straight out.
- 8) Press a dry cotton ball on the injection site for a few seconds. Do not rub or massage the site.
- 9) Put the plastic cover back on the needle.
- 10) Throw away the needle, syringe, Mixject Vial Adapter, and the used vials in a safe, hard-walled container, according to your physician's instructions and the laws of your state.

What is the proper use of needles and syringes?

Needles, syringes, and vials should be used for only one injection each. Place all used syringes, needles, and vials in a hard-walled plastic container, such as an empty liquid laundry detergent container. Keep the cover of this container tight and out of the reach of children. When the container is full, check with your doctor or nurse about proper disposal, as laws vary from state to state.

How should COPAXONE® and the sterile water (diluent) be stored?

Store the brown vials of sterile, lyophilized material for subcutaneous injection COPAXONE® in a refrigerator (36-46° F / 2-8° C). If you cannot have refrigerator storage, COPAXONE® can be stored at room temperature (59-86°F / 15-30°C) for up to one week. Do not store COPAXONE® at room temperature for longer than one week. Avoid exposure to higher temperatures or very bright light.

The clear vials of sterile water (diluent) may be stored at room temperature.

What is the shelf-life of COPAXONE®?

Do not use COPAXONE® after the expiration date (EXP) printed on the vial label.

COPAXONE® does not contain preservatives. Therefore, it should be used right away after you reconstitute (mix) it. If you cannot use it right away after reconstitution, throw it away.

Manufactured For:

TEVA Neuroscience LLC

Kansas City, MO 64134

Manufactured By:

Ben Venue Laboratories

Bedford, OH 44146

or

TEVA Pharmaceutical Industries, Ltd.

Kfar-Saba, 44102, Israel

Rev.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-622/S-015

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	20,622 (015)
Sponsor:	TEVA
Drug:	COPAXONE
Proposed Indication:	Multiple Sclerosis
Material Submitted:	New Protocol 9003
Correspondence Date:	
Date Received / Agency:	
Date Review Completed	
Reviewer:	Gerald Tremblay, MD

Summary

Copaxone® (glatiramer acetate) is a copolymer of 4 L-amino acids (glutamic acid, alanine, lysine and tyrosine) in fixed proportion arranged randomly in molecules of random weights ranging from 4700 to 11,000 Dalton. It is indicated as a daily, 20 mg subcutaneous injection for the reduction of relapses in relapsing-remitting multiple sclerosis.

Copaxone® was approved in 1996 based on two randomized, double-blind, placebo-controlled, clinical trials. The first study was done at a single center and involved 50 subjects who were examined every three months for two years. The primary endpoint was the proportion of patients who remained exacerbation free during the trial. 56% of the Copaxone® group remained relapse free compared with 28% of those on placebo ($p = 0.085$). Mean relapse frequency differences were significant ($p = 0.005$).

The second study (01-9001) was multicenter, randomized, double-blind and placebo-controlled had a design similar to the first. Its primary endpoint was the mean 2 year relapse rate, which was 1.19/2 years for the Copaxone® group and 1.68/2 years for the placebo group ($p = 0.055$).

The most common adverse events associated with Copaxone® include an injection site reaction (pain, swelling and redness) in about 70% of patients, chest pain in about 26%, and an immediate-post injection reaction (chest tightness, flushing, dyspnea, anxiety, urticaria, palpitations) in about 10% of patients.

The protocol to be reviewed here, 9003, employs MRI endpoints to compare Copaxone® to placebo in patients with relapsing-remitting MS. The sponsor states, "The goal of the study was to determine whether the already proven clinical effect of COPAXONE® on disease activity is also reflected by changes in MRI parameters and what is the time course of the development of treatment effect. The open-label phase was aimed to evaluate the durability of the effects seen during the initial blinded phase."

The sponsor requests labeling amendments to include data from protocol 9003 []

[] This is a review of the MRI protocol (9003) and the proposed labeling changes.]

Title	A Multi-National, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study, Extended by Open-Label Treatment, to Study the Effect of COPAXONE® (Copolymer-1) on Disease Activity as Measured by Cerebral Magnetic Resonance Imaging in Patients with Relapsing-Remitting Multiple Sclerosis (Protocol 9003)
Objectives	To determine effect of Copaxone® on MRI parameters
Duration	9 months (followed by 9 mo open-label)
Sample Size	239 patients were randomly assigned to 119 on COPAXONE® and 120 on placebo. There were 14 patients who dropped out of the trial prematurely, and 225 patients completed the trial.
Setting	29 European centers in Belgium, France, Germany, Holland, Italy, and the UK and Canada participated in an outpatient setting. All MRIs were performed at the local institution but, for purposes of this protocol, were sent to Milan for analysis
Inclusion Criteria	<ol style="list-style-type: none"> 1. Clinically definite MS of relapsing remitting type (RR-MS), as defined by Poser et al., for at least 1 year. (This requirement was later amended (Amendment No. 5) so that patients who had been diagnosed less than 1 year prior to entry but had their first attack within the last 12 months prior to trial initiation, were also eligible for participation.) 2. The patient had to be ambulatory with a Kurtzke EDSS score within the range of 0-5 with at least one documented relapse in the two years prior to study initiation. 3. At least one Gd-enhancing lesion in the screening MRI scan. 4. Off steroids and relapse-free for at least 1 month before screening MRI. 5. Patient had to be between the ages of 18 and 50 years old, inclusive. 6. Patient had to be willing and able to give informed consent. 7. Women of pregnancy potential had to practice birth control
Exclusion Criteria	<ol style="list-style-type: none"> 1. Prior use of COPAXONE® and oral myelin (<i>later amended</i>) 2. Prior total lymphoid irradiation in the last 2 years before study entry. 3. Prior use of immunosuppressant or cytotoxic agents last 2 years before study entry. 4. Use of immunosuppressive agents, including chronic corticosteroids or ACTH within the last 6 months before study entry. 5. Short-term use of corticosteroids or ACTH within 30 days of the screening visit. 6. A relapse between screening visit and entry. 7. A life-threatening or clinically significant disease. 8. Medical or psychiatric conditions affecting ability to consent or participate in study. 9. Known allergy to gadopentetate dimeglumine or to mannitol. 10. Patient unable to undergo repeated MRIs.
Study Schedule	Monthly MRIs
Outcome Measures	<p>Primary endpoint: the sum, per patient, of the T1 Gd-enhancing (positive T1-MRI) lesions counted during the nine months of the double-blind period.</p> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> ▪ the <i>proportion</i> of treated patients with positive T1-MRIs; ▪ the total <i>volume</i> of lesions on positive T1-MRIs; ▪ the total number of <i>new</i> lesions on positive T1-MRIs; ▪ the total number of new lesions on positive T2-MRIs; ▪ the total <i>volume</i> of lesions on positive T2-weighted MRIs; ▪ the total volume of <i>hypointense lesions in unenhanced T1-MRIs</i>;
Analysis Plan	The total number of Gd-enhancing lesions will represent the sum of these lesions counted [per patient] in all scans performed during the 9 month double blind period. An analysis of baseline adjusted covariance will be used to compare the two groups in this end-point. Covariates that will be used in the analysis are MRI parameters assessed at screening and at baseline, characteristics such as baseline EDSS, number of relapses in the year prior to trial entry and disease duration. Demographic data including age and sex will also be used as covariates in the analysis.
Reported Result	The total number of Gd T1-MRI lesions reduced by 29% (adjusted mean), LOCF analysis. Mean difference over placebo was -10.84 (95% CI -17.97, -3.71), p = 0.0032.

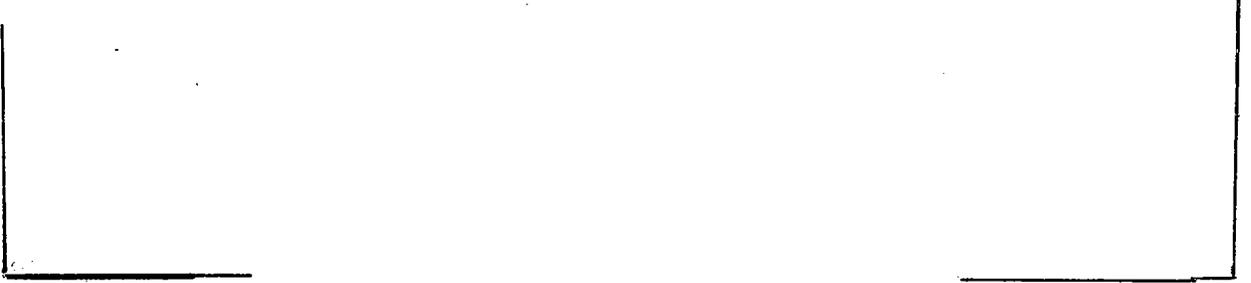
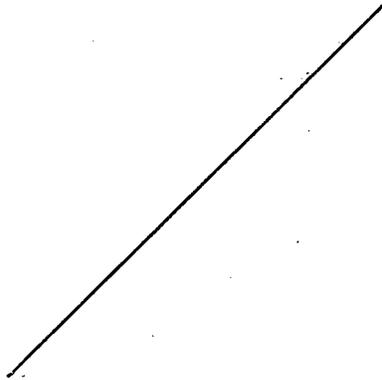
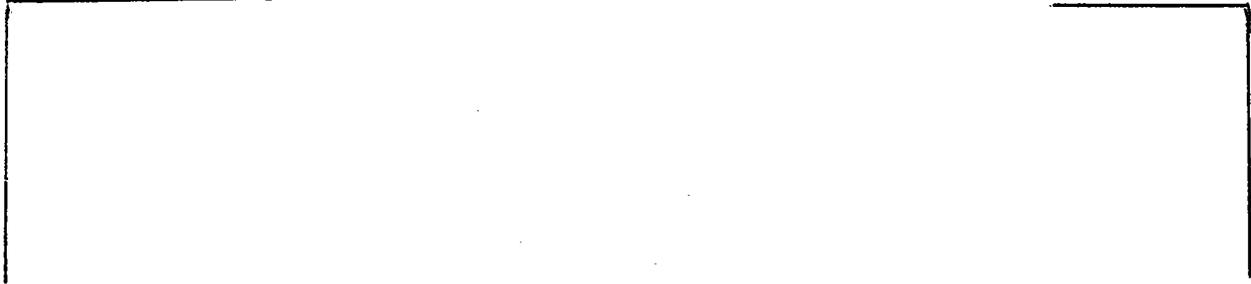
Table of Contents

This review has two parts. The first part consists of a review and analysis of a recent TEVA-sponsored MRI trial (9003) of glatiramer acetate (COPAXONE®) in multiple sclerosis. The second part reviews the changes that TEVA is proposing to its current COPAXONE® labeling

Summary	1
2. Introduction: A New Protocol and Label for COPAXONE®	6
3. Background: MRI Principles and Their Application to Multiple Sclerosis	7
3.1 Basic MRI Principles	7
3.2 Different Weighting Schemes Used in MRI	8
3.3 Contrast Enhancement on MRI with Gadolinium	9
3.4 Using MRI to Demonstrate Efficacy in MS Trials	9
4. Protocol 9003: The Effect of COPAXONE® on the MRI in MS	11
4.1 Title	11
5. Objectives	11
5.1 Primary	11
5.2 Secondary	11
6. Design	11
6.1 Duration	12
6.2 Sample Size	12
6.3 Setting	12
6.4 Key Inclusion Criteria	12
6.5 Key Exclusion Criteria	13
6.6 Protocol Amendments	13
6.7 Concomitant Medications	14
6.8 Randomization and Analysis of Potential Confounding Variables	14
6.9 Dosage	14
6.10 Study Schedule	15
6.11 MRI Methodology	16
6.11.1 Definition of a "lesion"	16
6.11.2 Sources of variability in MRI method how they were minimized	16

6.12	Sample Size Rationale	19
6.13	Outcome Measure	19
6.13.1	Primary	19
6.13.2	Secondary	19
6.14	Safety Monitoring and Analysis	19
6.15	Analysis Plan for the Efficacy Endpoints	20
6.15.1	Interim Analyses and p-values	20
6.15.2	Adjusting for Dropouts and Missing Data	20
6.15.3	Analysis of the Primary Endpoint (Total Lesions, Gd T1-Weighted)	21
6.15.4	Analysis of Secondary Endpoints	21
7.	Results	22
7.1	Protocol Violations	22
7.2	Treatment of Exacerbations During the Trial	22
7.3	Quality Assurance in MRI Performance and Interpretations	23
7.4	Dropouts	23
7.5	Confounding Variables	23
7.6	Key Finding	24
7.7	Secondary Efficacy Parameters	24
7.7.1	The Proportion of T1 Gd-Enhancing Lesion-Free Patients	24
7.7.2	T1 Gd-Enhancing Lesion Volume	25
7.7.3	The Total Number of New T1 Gd-Enhancing Lesions	26
7.7.4	T2 Lesion Volume	26
7.7.5	Number of New T2 Lesions	26
7.7.6	Hypointense Lesion Volume on Unenhanced T1 Images	27
7.7.7	Clinical Effects	28
7.8	Safety Parameters	28
7.8.1	Injection Site Reactions (ISRs)	29
7.8.2	The Immediate Post-Injection Reaction & Chest Pain	29
7.8.3	Deaths and Serious Unlabeled Events	29
8.	Sponsor's Conclusions on Protocol 9003	30
9.	Reviewer's Comments on Protocol 9003	31
9.1	Comments on Informed Consent Issues	31
9.2	Comments on Protocol Amendments	34
9.3	Comments on the Primary Endpoint (total number of T1 Gd-enhancing lesions)	36
9.4	Comments on Secondary Endpoints	37
9.5	Comments on Sponsor's Conclusions Regarding Clinical Results	38
9.6	Overall Comments and Conclusion on Protocol 9003	39

10. Proposed Labeling Changes: Background	40
10.1 Administrative History	40
10.2 Applicable Administrative Regulations and Guidelines	40



Appendix:

Staff Training _____ 65

1. Introduction: A New Protocol and Label for COPAXONE®

COPAXONE® (glatiramer acetate) was approved for the treatment of relapsing-remitting multiple sclerosis (RR-MS) in 1996. For a primary end point of the rate of relapses, a 29% reduction is typical, with a trend towards a greater effect on less disabled MS patients.¹ Interferon beta-1b (Biogen's Betaseron®) similarly reduces the frequency of relapses in this population.² COPAXONE® provides little benefit to highly disabled patients or those with progressive types of MS, therefore the focus with the drug has been on reducing the rate of relapses in less disabled patients having RR-MS.

MRI has been proposed as a vital adjunct in MS diagnosis³. It has also become a recommended way to monitor MS patients chronically. MRI shows the extent of the patient's MS pathology and "burden of disease" at the time the MRI is performed better than neurological examination. As a research tool, Wolinsky commented at the time the previously cited COPAXONE® study was published, "The limited size of the cohort of patients studied with serial MRI in the copolymer I study was inadequate to detect a significant drug effect on lesion activity or *accumulated burden of disease*. An adequately powered study to specifically address *this paraclinical measure* of disease activity [MRI] would be applauded."⁴ It therefore has become desirable to link MRI, felt by some to be the best tool for MS diagnosis and monitoring, with a drug previously shown to be clinically efficacious. As a practical and economic matter, the fact that MRI endpoints have already been used to support efficacy with interferon beta-1b (Biogen's Betaseron®)⁵, similar data on COPAXONE® will aid in comparing the relative efficacy of the two MS drugs.

A new protocol, designated 9003, was undertaken to see if COPAXONE® decreases the number of gadolinium (Gd) enhancing lesions in the T1-weighted images of MRIs in patients with relapsing-remitting multiple sclerosis (RR-MS). In the words of the sponsor: "The goal of the study was to determine whether the already proven clinical effect of COPAXONE® on disease activity is also reflected by changes in MRI parameters and

¹ Johnson KP, Brooks BR, Cohen JA, et al. Copolymer I reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology* 45:1268-76, 1995.

² The IFNB MS Study Group and the Univ British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. *Op. Cit.*, 1277-85.

³ Fazekas F, Barkhof F, Filippi M, et al. The contribution of magnetic resonance imaging to the diagnosis of multiple sclerosis. *Neurology* 53:448-456, 1999.

⁴ Wolinsky JS. Copolymer I: A most reasonable alternative therapy for early relapsing-remitting multiple sclerosis with mild disability. *Neurology* 45:1245-47, 1995, citation to an early abstract in which Copolymer I is evaluated using MRI, deleted, emphasis added.

⁵ IFNB (Note 2, above), op cit.

what is the time course of the development of treatment effect. The open-label phase was aimed to evaluate the durability of the effects seen during the initial blinded phase.”⁶

The primary purpose of this review is to present and evaluate the design and results of Teva’s COPAXONE® MRI protocol 9003. The secondary purpose is to determine whether the results of 9003

support the sponsor’s proposed labeling changes. My plan is to first provide some MRI principles as background, since MRI parameters are the primary and the secondary endpoints. I will then describe the 9003 study and its results. Next I will comment on the design and the sponsor’s analysis.

The last section of this review will focus on proposed labeling changes, by which sponsor seeks to add the 9003 results

2. Background: MRI Principles and Their Application to Multiple Sclerosis

As discussed in the Introduction (Section 2, above), the MRI has become, at least according to some radiologists and MS experts, the gold standard for diagnosis and management of MS. The test has also become the accepted means of showing that a drug is efficacious in MS⁷, the most notable example being its use in the interferon beta-1b trial cited above⁸. A review of the use of MRI in MS will help the reader understand the basis for sponsor’s choice of MRI endpoints. Furthermore, understanding the different kinds of information that can be obtained from different MRI techniques may help understand the pros and cons of allowing claims to be made with respect to secondary endpoints (all of which are MRI-based).

2.1 Basic MRI Principles

MRI is the most sensitive way to detect MS lesions, which are often asymptomatic, in living patients.⁹ Paty states it is five times more sensitive than any clinical measure.¹⁰ The technique relies upon the abundance of protons (positively charged hydrogen nuclei) in tissues. Each proton may, for the sake of this explanation, be imagined as infinitesimally

⁶ Protocol 9003 Final Report, July 2000, p. 46.

⁷ Ellison GW, Recent Advances and Future Challenges in Multiple Sclerosis Clinical Trial Design, in Multiple Sclerosis: Advances in Clinical Trial Design, Treatment and Future Perspectives, Goodkin DE and Rudick RA (Eds.), Springer, London, 2, 1996.

⁸ Id.

⁹ Fazekas F, et al., op cit.

¹⁰ Paty DW. The interferon beta-1b clinical trial and its implications for other trials. Ann Neurol 36:S113-S114 (1994).

small, magnetic, sphere that is spinning about its axis. If one places something with a large number of protons, e.g., someone's brain, in a strong magnetic field, the axis of protons will tend to align themselves along the axis of the magnetic field. The alignment is not rigid, however. The axis of each spinning proton precesses, or wobbles, at a specific frequency that is determined by the strength of the magnetic field. Note that the magnetic field, measured in Tesla, is a characteristic of the MRI machine and is known. The proton's environment, on the other hand, is unknown. *It is precisely the proton's environment that we are trying to learn about when we use MRI.* In other words, if we can learn its wobble frequency, we will know its environment. And if we can learn its environment (which we will display in the form of a visible image), we can tell whether the proton resides within healthy or diseased tissue.

To learn what the proton's environment is, will require more than simply placing it in a strong magnetic field, however, and depends on the physical phenomenon of nuclear resonance. (The old name for MRI was NMR, nuclear magnetic resonance.) If one applies a spectrum of external radio frequencies that include the one at exactly the same energy with which the proton wobbles – with which it resonates -- the proton will absorb that particular frequency and tilt out of alignment, reaching a higher energy state. But when the radio signal is stopped, the proton falls back to its former state of (wobbly) alignment in the magnetic field, emitting its characteristic radio frequency – its resonance frequency -- as it does so. The MRI scanner's antennae, commonly called its "coils," pick up this emitted radio energy.

From the resonance frequencies emitted by countless numbers of individual protons and the known magnetic field strength, a computer program can compute the nature and environment of the protons in any area of tissue. After the protons' average nature and environment are computed for each of many tiny volume elements (voxels) of tissue, an image can be generated, an MRI image. The greater the number and smaller the size of the voxels, the better the image quality (resolution), but imaging time and computer processing time will be the price paid.

2.2 Different Weighting Schemes Used in MRI

When radio signals are stopped during MRI imaging, the protons go back to their former, lower energy state, also called the "resting state" with different "relaxation times" depending on their environment. Relatively quick relaxation times are referred to as T1 and relatively late ones as T2. The images can be weighted or biased in favor of one or the other or in between, to create *T1-weighted, T2-weighted or proton-density weighted images*, respectively. It is also possible to manipulate how the radio pulses (the pattern is called a "pulse sequence") are delivered to the tissues. One variable is the time between each radio pulse, called the repetition time (TR). Another useful pulse sequence employs trains of repetitive radio pulses to generate "echoes" at specific echo times (TE).

To create T1-weighted images one uses a short TR, and using long TEs creates T2-weighted images. Mixing these parameters can produce proton-density-weighted images. As a general rule, T1-weighted images are particularly good for showing anatomical details, and T2-weighted images are better for pathological changes in tissue. Cerebrospinal fluid is best distinguished from brain with proton-density weighted images.

2.3 Contrast Enhancement on MRI with Gadolinium

Gadolinium DTPA is an intravenous contrast agent with paramagnetic qualities that enhance the contrast between adjacent tissues having otherwise similar T1 and T2 relaxation times. By decreasing these relaxation times, visual discrimination is accentuated. It is particularly useful in demonstrating disruptions in the blood-brain barrier. It is used mainly to enhance T1 scans, and that is the case in this protocol.

2.4 Using MRI to Demonstrate Efficacy in MS Trials¹¹

T2-weighted images, in which the number, size and other features were measured, were used at first when the MRI was introduced as a way of measuring treatment efficacy. The disadvantage of T2-weighting was the waiting; it could take years to show a difference between drug and control groups. The emphasis then shifted to doing frequent, serial scans to look for relapses, i.e., new or enlarging lesions.

Currently, investigators rely on sequential (monthly or bimonthly) gadolinium enhanced, T1-weighted scans (Gd T1-MRI) because the areas of "enhancement correlate better with clinical phenomena and appear to be more responsive (sensitive to change) more quickly than T2-weighted 'lesions'."¹² Evidence of drug efficacy may be shorted to months with Gd T1-MRI instead of the years required for the older way of using MRI.

Lesion volume is another method of monitoring patients. In theory, one can add the volumes of all lesions and obtain a total "burden of disease," which tends to increase gradually in MS patients. Unfortunately, the edges of lesions are ill-defined, so there is an unacceptably high level of inter-observer variation. Intra-observer variation can be acceptable, however. Ultimately, automated or semiautomated methods will reduce the variability in volume measurements further.¹³

The number and area of Gd T1-MRI lesions increases during relapses.¹⁴ High-dose steroid treatment may alter the appearance of the lesions transiently, but the appearance

¹¹ Ellison GW, id. (providing a history of MRI use in MS trials).

¹² Id. at 3.

¹³ Id.

¹⁴ Id.

may revert when the drug is stopped. Steroids also probably affect inflammation and blood-brain barrier permeability more than demyelination, because T2-weighted images (which show chronic changes) are minimally affected by steroid treatment.¹⁵

MRI abnormalities do not correlate well with the disability score in MS patients, nor does MRI have much predictive value for a patient.¹⁶ Presumably this is due to a lack of sensitivity of our clinical assessment techniques in some patients¹⁷ and the importance of the location of the lesion on the disability. That is, numerous small lesions scattered throughout the white matter of both hemispheres may cause fewer obvious symptoms than a single lesion strategically placed in the brainstem. Newer methods such as *magnetization transfer imaging* (MTI) appear to be an improvement over T2-weighted and Gd T1-weighted MRI, because it distinguishes among the many types of pathology that may be present in MS patients.¹⁸

Table: Summary of the 7 Radiographic Objectives Determined by Protocol

WEIGHTING	CONTRAST	METHOD	MISSES	SHOWS
T1	With Gd	Number	Chronic, uninfamed lesions	Acute inflammation & breakdown of BBB
T1	With Gd	Proportion	As above	As above
T1	With Gd	Volume	As above	As above
T1	With Gd	New number	As above	As above
T2	Without Gd	New number	Some lesions missed; Unable to differentiate pathologies	Most lesions; = Chronic
T2	Without Gd	Volume	As above	"burden of disease"
T1	Without Gd	Volume of hypointense Lesions ("Black holes")		Chronic, severe tissue disruption

¹⁵ Id.

¹⁶ Id. citing evidence that suggests that MRI may or may not correlate with disease activity; See Khoury SJ, et al., Longitudinal MRI in multiple sclerosis: correlation between disability and disease burden. *Neurology* 44 (Supp 11):2120-2124, 1994.

¹⁷ Noseworthy J, Van der Voort M, Wong C, et al. Interrater variability with the expanded disability status scale (EDSS) and functional systems (FS) in a multiple sclerosis clinical trial. *Neurology* 40:971-975, 1990.

¹⁸ See, e.g., Filippi M, Inglese M, Rovaris M, et al. Magnetization transfer imaging to monitor the evolution of MS: A 1-year follow-up study. *Neurology* 55:940-946, 2000.

3. Protocol 9003: The Effect of COPAXONE® on the MRI in MS

3.1 Title

A Multi-National, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study, Extended by Open-Label Treatment, to Study the Effect of COPAXONE® (Copolymer-1) on Disease Activity as Measured by Cerebral Magnetic Resonance Imaging in Patients with Relapsing-Remitting Multiple Sclerosis

4. Objectives

4.1 Primary

To determine the *total number of Gd-enhancing lesions in T1-weighted MR images (Gd T1-MRI)* in MS patients treated with 20 mg per day of COPAXONE® for 9 months.

4.2 Secondary

To determine:

- the *proportion* of treated patients with positive T1-MRIs;
- the total *volume* of lesions on positive T1-MRIs;
- the total number of *new* lesions on positive T1-MRIs;
- the total number of new lesions on positive T2-MRIs;
- the total *volume* of lesions on positive T2-weighted MRIs; and
- the total volume of *hypointense lesions in unenhanced T1-MRIs*.

5. Design

Protocol 9003 was designed as a multi-national, multi-center, randomized, double-blind, and placebo controlled for 9 months. For the subsequent 9 months, all patients took the drug and the design became open-label. The first patient was enrolled on March 12th, 1997 and the last on November 23rd, 1997. Eligible patients had to have clinically definite relapsing-remitting multiple sclerosis (RR-MS), an EDSS score between 0 and 5, a documented relapse in the 2 years prior to study initiation and at least one Gd-enhancing lesion on the screening T1-MRI.

Patients were randomized into two groups that received either 20 mg sq COPAXONE® with 40 mg mannitol or placebo (40mg of mannitol) daily. MRIs were done monthly during the blinded phase and every 3 months during the open label phase.

5.1 Duration

The blinded phase lasted 9 months (36 weeks) and was followed by an open-label phase of the same duration for a total of 18 months.

5.2 Sample Size

239 patients were randomly assigned to 119 on COPAXONE® and 120 on placebo. There were 14 patients who dropped out of the trial prematurely, and 225 patients completed the trial. Of the 14 dropouts, 7 were in the placebo group and 7 in the drug group. Dropouts and their effect on data analysis are discussed in the Results section, below.

5.3 Setting

29 European outpatient centers in Belgium, France, Germany, Holland, Italy, and the UK and Canada participated in an outpatient setting. All MRIs were performed at the local institution but were sent to the [] for analysis. Radiologists and technicians at the [] performed all of the lesion identification, lesion counting, outlining of lesions and volumetry.

5.4 Key Inclusion Criteria

1. Clinically definite MS of relapsing remitting type (RR-MS), as defined by Poser et al.¹⁹, for at least 1 year. (This requirement was later amended (Amendment No. 5) so that patients who had been diagnosed with RR-MS less than 1 year prior to trial entry, but had their first attack within the last 12 months prior to trial initiation, were also eligible for participation.
2. The patient had to be ambulatory with a Kurtzke EDSS score within the range of 0-5 with at least one documented relapse in the two years prior to study initiation.
3. At least one Gd-enhancing lesion in the screening MRI scan.

¹⁹ Poser, CM, Paty, DW, Scheinberg L, et al., New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 13:227-231, 1983.

4. Patient must be off steroids and relapse-free for at least 1 month before screening MRI.
5. Patient had to be between the ages of 18 and 50 years old, inclusive.
6. Patient had to be willing and able to give informed consent.
7. Women of pregnancy potential had to practice birth control.

5.5 Key Exclusion Criteria

1. Prior use of COPAXONE® or Oral Myelin (later amended; see section 6.6, item 4, below).
2. Prior total lymphoid irradiation in the last 2 years before study entry.
3. Prior use of immunosuppressant or cytotoxic agents last 2 years before study entry, such as cyclophosphamide, cladribine, or mitoxantrone.
4. Use of immunoactive agents, such as azathioprine, cyclosporine and including chronic corticosteroids or ACTH within the last 6 months before study entry.
5. Short-term use of corticosteroids or ACTH within 30 days of the screening visit.
6. A relapse between screening visit and entry (i.e., baseline).
7. A life-threatening or clinically significant disease.
8. Medical or psychiatric conditions affecting ability to consent or participate in study.
9. Known allergy to gadopentetrate dimeglumine or to mannitol.
10. Patient unable to undergo repeated MRIs.
11. Pregnancy or lactation.

5.6 Protocol Amendments

There were eight amendments to the protocol:

1. Eliminating the requirement of intra- and inter-observer reproducibility. Originally, 5% intra- and inter-observer reproducibility was required, but was later deleted, "since the training exercise of MRI-AC is performed prior to study initiation in order to check inter and intra-observer variability." (Amendment 1).
2. Allowing use of chronic ACTH, chronic corticosteroids (not including treatment of acute exacerbations) and immunoactive agents such as Azathioprine, cyclosporine, interferons, Deoxyspequaline, anticytokines, TNF-a, or sulfasalazine in the 6 months prior to entry. (Amendment 2).
3. Changing the term "chronic steroids..." to "systemic chronic steroids..." Chronic defined as continuous for 1 month or repeated monthly or weekly ACTH or steroid in past 6 months prior to entry. (Amendment 3).
4. Permitting participants in Oral Myelin Study to enroll. (Amendment 4)
5. Altering the duration of previous MS diagnosis. Patients need only have been diagnosed with RR-MS and the "documented onset of the first attack within 12 months prior to study entry is available." (Amendment 5).
6. Altering the injection technique.
7. Altering the method of visual examination.

8. Altering the trial duration from two 9 month phases to up to 30 months.

5.7 Concomitant Medications

Permitted:

Short-term (up to 3 days) corticosteroids during acute relapses of up to 1000 mg/day of IV methylprednisolone. Symptomatic treatment with anti-cholinergic and spasmolytic drugs were permitted.

Not Permitted (Later modified by Amendments, see Section 6.6, above)

- Other investigational forms of therapy
- Interferon treatment
- Systemic chronic corticosteroids
- ACTH (short-term or chronic)
- Chemotherapeutic agents
- Immunosuppressive or immunomodulating drugs

5.8 Randomization and Analysis of Potential Confounding Variables

Patients were allocated into treatment group or placebo group according to a stratified (by centers) permuted block method that had been prepared using the SAS® random number generator. Treatment allocation did not use the same block for more than 1 medical center. (The protocol did not describe how investigators received the randomization code, i.e., whether they needed to call the data analysis center at the time of each patient enrollment or had the random numbers in advance.)

Analysis of potentially confounding variables is presented below. Briefly, however, the randomization procedure was successful in producing groups that were similar except for whether or not they received COPAXONE®. That is, the two groups were similar with respect to the baseline number of Gd T1-MRI lesions, EDSS, number of relapses of the past two years, disease duration, age or gender.

5.9 Dosage

Patients received a subcutaneous (sq) injection of 20 mg COPAXONE® with 40 mg mannitol or 40 mg mannitol (placebo) as a single daily dose.

5.11 MRI Methodology

The MRI result formed the basis for all of the outcome measures in this protocol except for the last (neurological examination). The term "lesion" was defined in advance. The MRI methods and quality assurance were also described by protocol prior to study initiation.

5.11.1 Definition of a "lesion"

A "lesion" was defined as an area of enhancement seen on a given 3 mm axial image, that is referable neither to a normally enhancing structure or contrast migration within the vessels. T2-weighted images were used as reference for analysis. Lesions contiguous in 3-mm axial slices were counted once.

5.11.2 Sources of variability in MRI method how they were minimized

The primary outcome measure in this protocol is the number of Gd T1-MRI lesions. That key number, however, depended on the imaging method and the field strength of the MRI magnet used. Thin slices, for example, are more likely to discriminate small lesions, for example. Likewise, an MRI magnet with a field strength greater than 1 Tesla is more likely to demonstrate small lesions than a weaker magnet. The dose of the contrast agent (Gd—gadolinium) may also affect whether lesions can be seen or not, as does the timing of the imaging with respect to the contrast infusion. If one is to measure relative changes among many small lesions (MS patients may have dozens or even hundreds of lesions), the slice angle and head position cannot change between studies²⁰.

Even when all the technical factors are controlled, there remain the difficulties of interpretation. MS lesions have ill-defined borders which makes an accurate evaluation of their area or volume difficult. The appearance of an MS lesion is non-specific; there are numerous other pathologic (and a few normal) conditions that may look like an MS lesion on MRI.

In summary, the key methodology of this protocol is MRI interpretation, or, more specifically, lesion counting and measuring. It is therefore important that the way the investigators controlled for the sources of variability (test error) be examined. The different sources of potential variation are 1) intra- and inter-observer variation and 2) instrument and methodology (MR imaging and interpretation methods) variations.

²⁰ Fazekas F, et al., op cit.

5.11.2.1 Intra- and inter-observer variations and their management

Intra- and inter-observer variability in reading the MRIs was, by protocol, to have been minimized by having all MRI interpretation be done at one central location in [redacted] by a group of radiologists. After MRIs were performed at one of the 29 participating centers, the copies were printed on standard radiographic film and digital tape and transferred to [redacted]

The neuroradiologist in [redacted] inspected them on an ordinary light box. He or she identified the lesions, marked them on a transparent overlay, and counted them. Results were placed on a standardized form. Technicians, who had been trained in the technique of outlining the lesions and using a computer program, were responsible for computing the lesions' volume.²¹ If the computer could outline a lesion, that approach was used. If, on the other hand, the lesion's edge was indistinct, the technician outlined it manually. The outline of the lesion was then passed to the computer program which calculated a lesion volume. Volume was computed only on lesions seen on three image types:

- Gd enhancing, T1-weighted images
- Hyperintense lesions on T2-weighted images
- Hypointense lesions on T1 or T2-weighted images

Quality assurance at the central reading facility in [redacted] was prescribed and amended in §7.5.4 (page 46) and Amendment 1 (June 26, 1997), respectively. The strikethrough text was eliminated by the amendment.

"On the first 30 scans accepted by the [redacted] (entry scan and 4 week scans), the neurologists will perform a separate exercise in order to check for lesion counting consistency. They will count enhancing T1-weighted lesions and new T2-weighted lesions on a computer display at the beginning of the study, 36 and 72, weeks later. Training of the technicians will be done before the beginning of the study, when 2/3 of the patients will have completed the placebo-controlled phase of the study and when 2/3 of the patients will have completed the open label phase of the study, using 2% of the total number of scans. ~~For all these measures the intra- and inter-observer reproducibility should be no greater than 5%.~~"

The reason given for elimination the last sentence is because "the training exercise of [redacted]"

²¹ "Lesion load measurements will be done by trained technicians following reference hardcopies where the lesions were marked by a neuroradiologist. The image analysis will be performed using a semiautomated segmentation technique based on the local thresholding (for T1-weighted hypointense lesion load manual outlining will be used)." (Protocol, ¶7.5.4)

- Different scanners with different field strengths (or other important characteristics) in use in different centers:

This factor was controlled for by requiring that scanners have at least 1.0 Tesla magnetic field strength, or, if less, be approved by the MRI Steering Committee.

5.12 Sample Size Rationale

The sample size was based on data collected from the published medical literature in which MRI had been used to monitor MS patients. Among those cited was also a paper describing a previous study of copolymer 1 in MS by Cohen. See Appendix A.1.1 Study Protocol, 17 July 1996, pp. 49-50.

5.13 Outcome Measure

5.13.1 Primary

The primary endpoint was the sum, per patient, of the T1 Gd-enhancing (positive T1-MRI) lesions counted during the nine months of the double-blind period.

5.13.2 Secondary

- the *proportion* of treated patients with positive T1-MRIs;
- the total *volume* of lesions on positive T1-MRIs;
- the total number of *new* lesions on positive T1-MRIs;
- the total number of new lesions on positive T2-MRIs;
- the total *volume* of lesions on positive T2-weighted MRIs; and
- the total volume of *hypointense lesions in unenhanced T1-MRIs*.

5.14 Safety Monitoring and Analysis

Adverse events (AEs) were defined in the protocol. (See, e.g., Appendix III, pp. 76-78, of the July, 1996 protocol.) Adverse events, adverse drug reactions (ADRs), adverse laboratory events, and degrees of seriousness are defined. A Serious Adverse Event (SAE), consistent with the generally accepted definition, is used. Intensity of the AE is graded mild, moderate or severe. Relation to study treatment (probable, possible and unclassified) terms are also defined. The COSTART nomenclature is used as a symptom/sign dictionary. SAE reporting is prescribed on page 64 of the protocol. At each clinic visit, the patient is queried as to any adverse experiences.

The statistical analysis section (page 52) describes how AE data are to be compiled and analyzed. Data will be tabulated by treatment group, gender, maximal severity, maximal outcome, action taken with the drug, and maximal relationship to the tested drug. SAEs were to be discussed and presented on a case-by-case basis. Laboratory abnormalities were to be compiled by frequency and compared between groups.

5.15 Analysis Plan for the Efficacy Endpoints

5.15.1 Interim Analyses and p-values

Two interim analyses for possible early termination were planned to be performed after at least 65 and 130 patients completed at least 36 weeks of the double-blind treatment. For the first interim analysis, the treatment effect was to be considered significant if the p-value were 0.00052334 or less. For the second interim analysis, it needed to be 0.014182 or less. The final analysis required a p-value of 0.045226. All p-values were derived from the O'Brien-Fleming correction to type I error. Only the end point (the total number of Gd-enhancing T1-weighted images) were analyzed in the interim analyses, and the ITT cohort and LOCF approach were used. (Final Data Analysis Plan, 19 October 1998, p. 4).

The p-values that were obtained at the first and second interim analyses were 0.0158 and 0.0131, respectively, using ANCOVA. The second p-value reached the predefined significance level, but the remaining weeks (in about 3 patients it was about 8 weeks) of the double blind part of the study were completed anyway.

5.15.2 Adjusting for Dropouts and Missing Data

The principal analysis cohort for efficacy and safety was the Intent to Treat (ITT) cohort. The Last Observation Carried Forward (LOCF) imputation scheme was used to account for early discontinuations or missing data.

An "As Is" data analysis was also done to rule out bias due to early withdrawals or missing data. Additional cohorts included the "Completers Cohort" and the "Evaluable Cohort." The former consisted of all patients who completed 36 weeks (+/- 4 weeks) of the double blind phase. (14 patients were excluded from this group of the 239 originally randomized.) The Evaluable cohort consisted of any patient who was neither excluded from the completers (in effect, a non-completer or dropout) nor any patient who was not compliant with the protocol, got steroids within 1 month of the screening MRI, missed a certain number of MRIs, etc. (See Id. at p 5). A total of 26 patients (which includes the 14 excluded from the Completers) were excluded from the evaluable cohort

"All trial end-points will be derived from the MRI measurements. No clinical efficacy parameters are planned to be calculated or assessed during the 9 month double-blind period due to the relatively short observation time which results in reduced statistical power to detect significant differences between groups." (Protocol of 17 July 1996, §8.9, page 53, emphasis added)

5.15.3 Analysis of the Primary Endpoint (Total Lesions, Gd T1-Weighted)

The primary end-point, the total number of T1 Gd-enhancing lesions, represented the sum of these lesions counted, per patient, in all scans performed during the 36 weeks of the double-blind period.

The protocol required a baseline adjusted analysis of covariance (ANCOVA, SAS PROC GLM) to be used to compare the two groups for the primary end-point incorporating terms for treatment and center. The treatment-by-center interaction term was not to be included in the model if it was not statistically significant (i.e. if $p > 0.05$). Covariates used in the analysis were the baseline pre-randomization number of Gd-enhancing T1-weighted lesions, baseline EDSS score, number of relapses in the 2 years prior to trial entry and disease duration. Demographic data including age and gender will also be used as covariates in the analysis." (Appendix b.1, Final Data Analysis Plan, 19 October 1998, p. 5).

In order to validate the results and conclusions of the above analysis, the following were to be performed: The log transformation for the total number of T1 Gd-enhancing lesions (+1), the rank transformation, and the mean value for the data as observed (AS IS) were applied and analyzed using the ANCOVA as specified above. The Quasi-Likelihood Poisson regression were to be similarly applied. (Id. at p. 7)

5.15.4 Analysis of Secondary Endpoints²³

Analysis of Secondary Endpoints	
Proportion of Lesion-Free Patients on T1-Weighted Images	Calculated for each visit and presented by visit and treatment group
Total Volume of Gd-Enhan. Lesions, T1-Weighted	Total lesion volume and change from baseline calculated each month. Repeated measures analysis of baseline adjusted covariance used to compare change from baseline between treatment groups.
Number New Gd-Enhan. Lesions, T1-Weighted	Same as primary endpoint

²³ See Protocol COP 9003: Clinical Trial Report, Final, July, 2000, Section 2.3; page 15.

Total Volume of Lesions, T2-Weighted	Same as for T1 lesion volumes, above.
Number New T2 Lesions	Same as for primary endpoint.
Volume Hypointense Lesions, T1-Weighted, No Gd	Same as for T1 lesion volumes, above.

6. Results

6.1 Protocol Violations²⁴

There were 9 types of protocol violations noted:

- Late consent (i.e., after screening visit)
 - 1 Pt., # 4513, copaxone group
- Use of immunomodulating drug in 6 mo prior to entry
 - 1 Pt, #3802, placebo group, 800 mg pentoxifylline po
- Marginal compliance with study medication < 70%
 - Pt. #3407, 41.6% compliance, placebo group
 - Pt. #3410, 38.6% compliance, copaxone group
 - Pt. #5501, 40.6% compliance, copaxone group
- Use of prohibited concomitant medications
 - 27 patients received steroids in violation of the protocol; those in the Copaxone® group got 27 steroid courses compared with 29 in the placebo group. Typically this was for allergic reactions or for unconfirmed "exacerbations" of MS. Looking only at high dose steroids (1000 gm IV methylprednisolone for 3 days), the Copaxone® group got 13 courses and the placebo group got 17 courses.
- MRI scans done too early or late (<21 or >35 days)
 - 35 patients
- Missed clinic visits
 - 21 patients
- Missed MRI scans
 - 27 patients missed at least some scans. The range was 1 to 7, and the average missed was 3.8 among those who missed any scans.
- Patient randomized out of order
 - 13 patients at 3 medical centers
- Other protocol violations

6.2 Treatment of Exacerbations During the Trial

High-dose (1000 mg IV daily for 3 days) methylprednisolone was given on one or more occasions to 79 patients in the double-blind part of the trial for a total of 114 confirmed

²⁴ Appendix C.2.3, vol. 11 of 18, p. 113

MS relapses. 68/114 were given to the placebo group and 46/114 to the Copaxone® group.

6.3 Quality Assurance in MRI Performance and Interpretations

Despite having procedures in the protocol, the amendment, and in separate protocols created over a year (through several revisions) at [redacted] for training and QA, I was unable to locate any documentation that the procedures were actually followed. The procedures themselves are not mutually consistent. The major concerns are variability among observers (especially intra-radiologist and inter-radiologist lesion count variability) and among the 29 MRI scanners.

6.4 Dropouts

239 patients were randomly assigned to 119 on COPAXONE® and 120 on placebo. There were 14 patients who dropped out of the trial prematurely, and 225 patients completed the trial. Of the 14 dropouts, 7 were in the placebo group and 7 in the drug group.

Reason for dropping out of trial	Number of patients
Consent withdrawn (personal reasons)	4 in drug group
Adverse event	2 in placebo group, 3 in drug group
Refusal to continue MRI scan	2 in placebo group
Lost to follow up	1 in placebo group
Other reason	5 in placebo group

6.5 Confounding Variables

Sponsor states that there were no significant differences between the COPAXONE® and placebo group. Sponsor states the mean age was 34 (range 19-50) and that there were “[n]o significant differences with respect to demographics, medical history, baseline disease characteristics or baseline MRI measurements as confirmed by statistical tests.” There were three times as many women as men. The time from diagnosis was 57 and 59 months for patients on COPAXONE® and on placebo, respectively. Baseline EDSS and number of relapses in the 2 years before trial entry were comparable between the two groups. P. 4

Table Covariates examined by sponsor

Covariate	Placebo Group n= 120	COPAXONE® Group n = 119
Baseline, pre-random. Number of Gd-T1-MRI lesions	Range 0 – 49 lesions Mean = 4.4 (SD 7.1) Median = 2.0 (Q1 = 1.0, Q3 = 5.5)	Range 0 – 23 lesions Mean = 4.2 (SD 4.8) Median = 3.0 (Q1 = 1.0, Q3 = 6.0)
Baseline EDSS	Min 0, Max 5	Min 0, Max 5

	Mean = 2.4 (SD 1.2) Median = 2.0 (Q1 = 1.5, Q3 = 3.3)	Mean = 2.3 (SD 1.1) Median = 2.0 (Q1 = 1.5, Q3 = 3.0)
Number Relapses in 2 years prior to trial entry	Min 1, Max 8 Mean = 2.5 (SD 1.4) Median = 2.0 (Q1 = 1.0, Q3 = 3.0)	Min 1, Max 12 Mean = 2.8 (SD 1.8) Median = 2.0 (Q1 = 2.0, Q3 = 3.0)
Disease (Months from diagnosis of MS)	Min 4, Max 274 Mean = 59.3 (SD 45.6) Median = 45.0 (Q1 = 30.0, Q3 = 79.5)	Min 3, Max 250 Mean = 57.4 (SD 46.7) Median = 44.0 (Q1 = 27.0, Q3 = 77.0)
Age	Min 18 yr, Max 48 yr Mean = 34 yr (SD 7.5)	Min 19 yr, Max 50 yr Mean = 34.1 yr (SD 7.4)
gender	Male 33 Female 87	Male 27 Female 92

6.6 Key Finding

For their result in Protocol 9003, sponsor states that the total number of Gd T1-MRI lesions was reduced by 29% (adjusted mean) following 9 months of COPAXONE® treatment compared with the placebo group, LOCF analysis. Mean difference over placebo was -10.84 (95% CI -17.97, -3.71), p = 0.0032.

	Placebo	Copaxone
Baseline, pre-random. Number of Gd-T1-MRI lesions	Range 0 – 49 lesions Mean = 4.4 (SD 7.1) Median = 2.0 (Q1 = 1.0, Q3 = 5.5)	Range 0 – 23 lesions Mean = 4.2 (SD 4.8) Median = 3.0 (Q1 = 1.0, Q3 = 6.0)
Sum of Gd T1-MRI lesions, ITT, LOCF²⁵	Range 0 – 386 lesions Mean = 36.3 (SD 53.5) Median = 17.0 (Q1 = 7.0, Q3 = 45.0)	Range 0 – 227 lesions Mean = 24.6 (SD 34.6) Median = 11.0 (Q1 = 6.0, Q3 = 32.0) p = 0.0018

6.7 Secondary Efficacy Parameters

6.7.1 The Proportion of T1 Gd-Enhancing Lesion-Free Patients

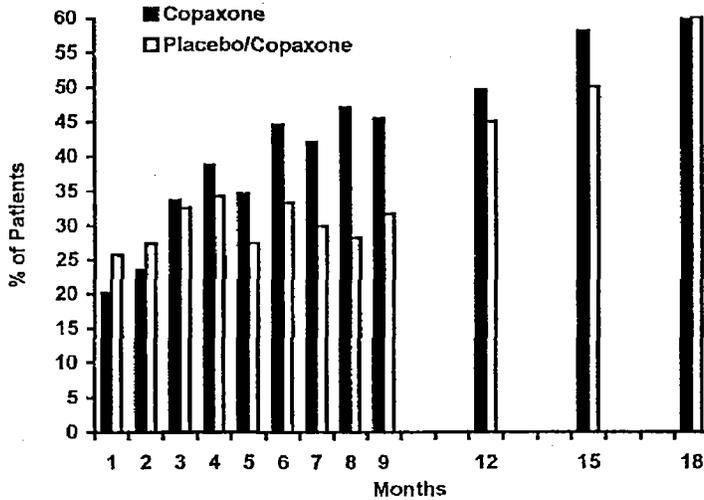
The proportion of lesion-free patients, according to sponsor, “is the complementary value of the proportion of Gd-enhancing lesions (the endpoint defined in the protocol).”

There was no significant difference between drug and placebo groups at the end of the 9-month double blind phase of the study with respect to the proportions of patients who were T1 Gd-enhancing lesion-free. On the other hand, the investigators point out that, in the last trimester, the Copaxone® group the difference became significant (p = 0.0008) (ld.) During the subsequent 9 month open-label phase, of those who had been on Copaxone® during the double-blind phase, about 60% became lesion-free about 6

²⁵ ITT, LOCF = Intent To Treat cohort and Last Observation Carried Forward imputation.

months into the open-label phase. By 9 months of open-label phase, patients in both groups had attained a 60% lesion-free level, as the following Figure 3 (page 26, Id.) suggests:

Figure 3: Proportion of T1 Gd-Enhancing Lesion-Free Patients by Month



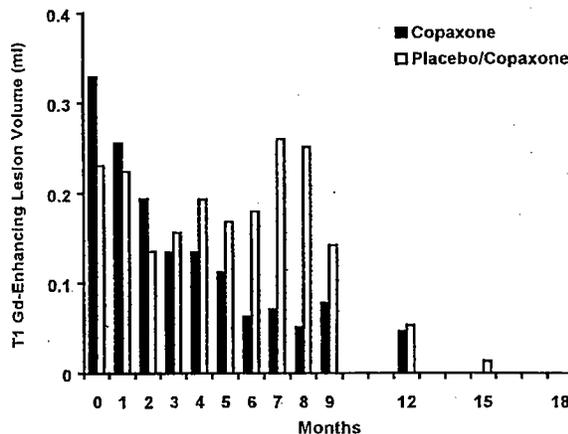
Cross-Reference: Appended Table, The Proportion of T1 Gd-Enhancing Lesions-Free Patients during Study by Month, Appendix C1.5.

Cross-Reference: Individual Data listing of the Total number of T1 Gd-Enhancing Lesions during the Study, Appendix C3.1

6.7.2 T1 Gd-Enhancing Lesion Volume

The investigators report that there was a change from baseline to month 9 in the volume of T1 Gd-Enhancing Lesions that was statistically different (Rank $p = 0.0102$) between drug and placebo groups, and those who got drug during the double-blind phase continued to show a reduction in lesion volumes during the open label phase. Figure 4 (Final Report, July 2000, page 27) illustrates their point:

Figure 4: Median T1 Gd-Enhancing Lesion Volume by Month



Cross Reference: Appended Table, T1 Gd-Enhancing Lesion Volume during the Study by Month, Appendix C1.6.

6.7.3 The Total Number of New T1 Gd-Enhancing Lesions

Sponsor reports that there was a reduction in the number of new lesions that was similar to that observed for the primary endpoint, i.e., there was a 30% reduction, adjusted mean, ITT cohort-LOCF analysis, $p = 0.0029$ at the end of the double-blind phase. (During the open-label phase summary statistics were not done on this endpoint. The lesions do not enhance long enough to be detected at the 3-month MRI interval of the open-label phase.)

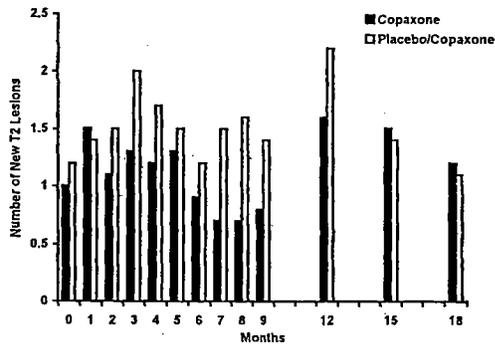
6.7.4 T2 Lesion Volume

This figure is sometimes called the "burden of disease" The lesion volume increased in both the drug and the placebo groups during the double-blind phase. The investigators state, however, that "[t]he mean change from baseline to Month 9 was lower in the Copaxone® group than that observed in the placebo group. The difference between treatment groups was statistically significance with $p = 0.0057$ on Rank." (Protocol 9003, Final Report, July 2000, page 29). Both groups continued to experience increases in lesion volumes during the open-label phase, but it was more (2.56 ml vs. 1.86 ml) in those who had received placebo during the double-blind phase. Sponsor concluded that the drug slows the rate of increase in lesion volume.

6.7.5 Number of New T2 Lesions

Sponsor reports a statistically significant difference between the two groups following the double-blind phase with respect to the number of new T2 lesions ($p = 0.0029$). The monthly mean number of new T2 lesions was 1.4 vs. 0.8 in the placebo and Copaxone® groups, respectively. Figures 6 and 7 are used to illustrate this point:

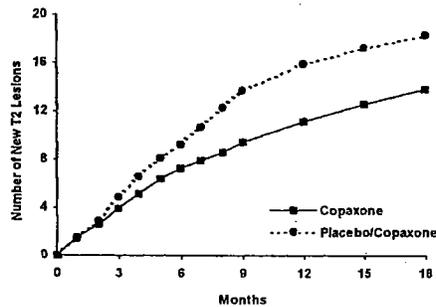
Figure 6: Mean Number of New T2 Lesions by Month



Cross-Reference: Appended Table: Total New T2 lesions during the Study by Month, Appendix C1.9.

Cross-Reference: Individual Data listing of Total Number of New T2 Lesions, Appendix C3.5.

Figure 7: Mean Cumulative Number of New T2 Lesions



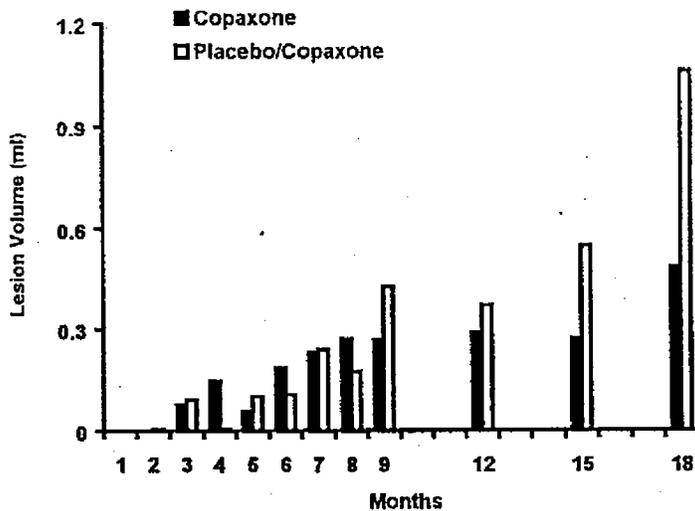
Cross-Reference: Appended Table, Cumulative New T2 Lesions during the Study by Month, Appendix C1.9.

Cross-Reference: Individual Data listing of Total Number of New T2 Lesions, Appendix C3.5.

6.7.6 Hypointense Lesion Volume on Unenhanced T1 Images

This MRI finding is thought to indicate acute inflammation. Sponsor does not report a p-value, but states that the trend over 18 months suggested that Copaxone reduced the rate of volume increase over time. See Figure 8 (Id. at p. 31):

Figure 8: Median Change from Baseline (Month 0) in Unenhanced T1 Hypointense Lesion Volume



Cross-Reference: Appended Tables, T1 Hypointense Lesion Volume during the Study by Month and the Change from Baseline (Month 0), Appendix C1.10.

Cross-Reference: Individual Data Listing of T1 Hypointense Lesion Volume, Appendix C3.6.

6.7.7 Clinical Effects

Four points are made by the investigators with respect to clinical effects (Id at pp. 33-34):

- The mean relapse rate was 33% lower for the drug group than the placebo group at the end of the 9-month double-blind phase.
- The EDSS score was unaffected by the drug. No patient progressed by this measure in either group.
- The drug did not affect the Ambulation Index.
- The relationship between the reduction in relapse rate and the number of Gd-enhancing T1 lesions on MRI was similar at about 30% compared to the placebo group. (This figure rose to 50% by the end of the open-label phase, according to sponsor.)

6.8 Safety Parameters

Among the well-known AEs with Copaxone the two most frequent patterns are described in current labeling. The first is the injection site reaction (ISR) and the other is an immediate post-injection reaction consisting of flushing, palpitations, dyspnea, anxiety, chest pain or tightness, constriction of the throat and urticaria. Both were reported in Protocol 9003.

6.8.1 Injection Site Reactions (ISRs)

Redness, swelling, pain and itching at the site of injection were far more common among subjects who received Copaxone® than those who received placebo in previously published studies.²⁶ Among the dropouts due to AEs, subjects 2201, 2204, 2901, 3805, and 5211 complained of the ISR, and it appeared to be the primary reason for dropping-out in subjects 2201, 3805, and 5211.

6.8.2 The Immediate Post-Injection Reaction & Chest Pain

In previous studies, the immediate post-injection reaction (flushing, palpitations, chest pain or tightness, throat constriction, etc), has occurred in at least 10% of patients.²⁷ In the present study, subjects 4507, 5208, 2204, 2901, 3403, 4405, 5503, and 5504 probably had this reaction. It caused early discontinuation (dropping out) in six of them (2204, 2901, 3403, 4405, 5503, 5504).

In two patients who dropped out (5503, 5504) the patients lost consciousness (or had a seizure) as part of the event. Subject 5504 had several episodes and lost consciousness for 15 seconds on two occasions before dropping out. In several of those who dropped out because of the immediate post-injection reaction (2204 and 2901), injection site reactions had also been a problem.

6.8.3 Deaths and Serious Unlabeled Events

6.8.3.1 A Death Associated with Hypereosinophilia

On February 17, 2000, Dr. Racoosin filed a review of an adverse event involving a patient death from hypereosinophilia syndrome. After 47 daily injections of Copaxone® the patient developed a rash over the extremities and back. The eosinophil count was markedly elevated at 150,000 (the normal absolute count is about 350), which increased to 227,000 about 3 months later despite prednisone therapy. She presented to the ER at that time with multiple infarcts on brain CT. She suffered a cardiac arrest and died after admission. Autopsy showed an acute pulmonary embolism, bilaterally and involving the major vessels, hypereosinophilic syndrome, and other incidental or secondary findings. The AERs database contained seven other reports of hypereosinophilia, but none of these to the degree reported in the present case.

The decedent's husband (a pharmacist) had his wife's drug analyzed by a private laboratory and it contained the four amino acids found in Copaxone® as well as an additional peak "of unknown identity that accounted for a substantial portion of the analyzed material (about 10%)."²⁸ DNDP was to follow up on the result of the outside chromatogram to see if the identity of the additional peak could be determined. The case was not felt to be due to a simple allergic reaction, because they do not result in such high eosinophil counts. The plan was to consult hematology, DNDP and to monitor for additional reports.

On May 11, 2000, Ann Farrell completed the hematology consult. She concluded the picture was consistent with either a primary idiopathic leukemoid reaction or a

²⁶ See, e.g., current labeling, table of AEs exceeding 2%.

²⁷ Id.

²⁸ Racoosin J, Review and Evaluation of Clinical Data, Adverse Event Report, Feb. 17 2000, page 2.

secondary one, but the elevated eosinophil count documented before she began taking Copaxone® suggested she may have had the idiopathic type. A causal link was felt unlikely and further monitoring was planned.

6.8.3.2 Cardiac Arrhythmia & Possible Myocardial Ischemia in Healthy Volunteer

In an ascending tolerability study involving 30 healthy male subjects, one subject (Number 101) received 20 mg of Copaxone® followed by increased heart rate, dizziness and palpitations.

With respect to subject 101, the symptoms could not be reliably reproduced despite injecting Copaxone® during a technetium perfusion scan. Sponsor concluded the cardiac event was not due to ischemia and believed it more likely to have been due to hyperventilation. (Chest pain as an AE will be discussed further in the labeling section.)

7. Sponsor's Conclusions on Protocol 9003

Sponsor concluded that Protocol 9003 demonstrated a positive effect of Copaxone® on objective MRI parameters and confirmed the drug's beneficial effect on relapse rate in RR-MS. The primary endpoint, the total number of T1 Gd-enhancing lesions, was reduced by 29% following nine months of Copaxone® treatment as compared with placebo.

The effect of Copaxone® on the number of active lesions seen on MRI, sponsor believes, becomes evident 2 months after the drug is started and becomes increasingly pronounced with the duration of treatment. "It is evident from the results of all MRI parameters and from the relapse rate that longer treatment with Copaxone® is beneficial to R-R MS [relapsing-remitting MS] patients." (Clinical Trial Report, Final, July 2000, page 48).

T2 lesion volume is slowed by Copaxone®, "thus affecting the total burden of disease, and stabilizes the number of new lesions seen on T2-weighted images over time." (Id.)

Sponsor also concludes that 9003 shows an effect on relapse rate. Specifically, the "reduction in the number of active lesions is accompanied by a comparable reduction in relapse rate that reaches statistical significance after nine months of treatment. The early onset of action is an important issue for the patients and may be an indicator for the clinical efficacy and potency of the drug." (Id.)

With respect to safety, sponsor states that Copaxone® is safe and well tolerated. Although AE's, particularly the injection site reaction, were common, they did not usually cause study withdrawal. Twelve patients withdrew because of AEs, 5 from the Copaxone® group and 7 from the placebo group.

8. Reviewer's Comments on Protocol 9003

8.1 Comments on Informed Consent Issues

The objective of Protocol 9003 was "to determine whether the already proven clinical effect of Copaxone® on disease activity is also reflected by changes in MRI parameters and what is the time course of the development of the treatment effect. The open-label phase was aimed to evaluate the durability of the effects seen during the initial blinded phase."²⁹ The objective raises the concern that human subjects were asked to participate in a medical experiment that was not necessary. The primary purpose was to look at the drug's effect on the MRI; the clinical question that Copaxone® reduces the rate of relapses in RR-MS was, in the sponsor's words, "already proven."

In "Ethical Considerations Raised by Clinical Trials," Richard Foa provides the essential ethical requirements for the conduct of MS clinical trials.³⁰ Key elements include a requirement that the information being sought be new and not available by other means. The benefits of the trial must outweigh the harms. Informed consent is required, and this consent must be "an expression... of a shared commitment with the investigator to the research goals."³¹ The Nuremberg Code, later codified in the Declaration of Helsinki, prohibits unnecessary human experimentation. "The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature."³²

Was the information being sought new and not available by other means? It may not have been known with certainty what effect Copaxone® would have on an MRI parameter as a primary endpoint, but the drug's effect on the rate of relapses in RR-MS was well-known. It was also well-known that MRI is far more sensitive in finding abnormalities in MS patients than any "clinical" tool (e.g., the neurological examination, the EDSS, AI, etc.) It is a logical inference, that if Copaxone® decreases the relapse rate by clinical measures (i.e., the relatively insensitive neurological examination), it would have a parallel effect on the more sensitive MRI. Foa states that "[t]wo-arm or multiarm clinical trials are grounded in the concept of equipoise."³³ That is, "there must be genuine uncertainty about the relative merits of the different treatment arms."³⁴ Protocol 9003 was not based on a genuine uncertainty that the placebo group would have fewer MRI lesions than the Copaxone®-treated group; it was already known that Copaxone® reduced relapses, and that relapses are associated with T1 Gd-enhancing lesions. It was to be expected that the clinically-effective drug would be associated with better MRI data.

Indeed, in the key Copaxone® trial, sponsor's Protocol 01-9001 involving 251 patients, one center (the [redacted] [redacted]) monitored MRI monthly. In those 27

²⁹ Protocol 9003, Final Report, July 2000, page 46.

³⁰ Foa R, Ethical Considerations Raised by Clinical Trials, in Goodkin DE and Rudick RA, eds., Multiple Sclerosis: Advances in Clinical Trial Design, Treatment and Future Perspectives, Springer, 1996, p. 336.

³¹ Id. at 337

³² THE NUREMBERG CODE [from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*. Nuremberg, October 1946 - April 1949. Washington D.C.: U.S. G.P.O., 1949-1953.]

³³ Foa, Id. at 342, citing Freedman B, Equipoise and the ethics of clinical research. N Engl J Med 317:141-145, 1987.

³⁴ Id.

patients, there was a significant ($p=0.03$) decrease reported in the number of T1 Gd-enhancing lesions.³⁵ Thus, there is an argument that what was being sought in this study was not new, nor was there equipoise with respect to the relative merits of the two treatment arms.

Could the information be found by alternative means? Given that there are several effective MS drugs available now, head-to-head comparisons (drug vs. active control) studies are likely to be needed. Combination therapy using two MS drugs vs. a single active control will also likely be subject to clinical investigation. Such studies are needed. Given the extreme sensitivity of MRI, the use of MRI endpoints in these trials would provide an alternate means of showing the (expected and probably already established) parallel between the MRI and clinical course. Animal models comparing Copaxone® to placebo and looking at MRI endpoints would be yet another alternative way to establish beyond doubt that a drug that has already been shown clinically effective in MS will have a similar effect on the MRI in treated patients. There is no need to perform yet another trial of an effective MS drug vs. placebo, however.

Sponsor may argue that Protocol 9003, by including neurological examinations, would be able to ascertain the relationship between MRI and neurological status in RR-MS patients treated with Copaxone® or placebo. Unfortunately, the protocol shows that there was never any intention to attempt definitive answers to clinical questions, particularly the correlation between MRI and clinical parameters.³⁶

Even if sponsor can overcome ethical concerns regarding the necessity of Protocol 9003, sponsor next stumbles on the problem of informed consent. Did the study participants voluntarily share the "commitment with the investigator to the research goals"? This commitment can only occur if the patients are told of the true purpose of the research, and this is an express element of informed consent.³⁷ In Protocol 9003, the stated purpose was "to determine the effect of a drug Copaxone® (copolymer 1) on disease activity in the brain."³⁸ A careful reading of *some* of the informed consent documents (they vary in significant ways among the 29 participating centers) would inform the astute reader that a large, well-designed clinical trial had already shown Copaxone® to be clinically effective, i.e. the "effect of ... Copaxone® (copolymer 1) on disease activity in the brain" reflected by clinical criteria was known. Thus, the astute reader of *some* of the forms may have been able to conclude that the primary purpose of the study was actually to study the MRI—not the already known clinical effects—in RR-MS. But many forms eliminated all reference to the most significant Copaxone® trial (9001). *In plain language, the purpose of 9003 was to determine the effect of Copaxone on the MRI; the clinical effect was already proven.* Prospective participants should have been told this. Because they were not, the required element of informed consent, a statement of purpose, was absent.

³⁵ Johnson KP, Bornstein MB, "Treatment of Multiple Sclerosis with Copolymer I," in Goodkin DE and Rudick RA, eds., Multiple Sclerosis: Advances in Clinical Trial Design, Treatment and Future Perspectives, Springer, 1996, p. 307. (Results later published in full in: Ge Y, Grossman RI, Udupa JK et al. Glatiramer acetate (Copaxone) treatment in relapsing-remitting MS: quantitative MR assessment. Neurology 54:813-17, 2000.

³⁶ See Protocol 9003, 17 July 1996, p. 18 (objectives), p. 55 (paragraph 8.10.0), and my discussion of secondary endpoint (clinical), below

³⁷ 21 CFR §50.25; ICH GCP Guideline § 4.8 (especially § 4.8.10); National Sciences and Engineering Council of Canada (NSERC) Ethical Conduct for Research Involving Humans, Article 2.4.

³⁸ See Informed Consents from the 29 centers, Vol. 34.4 of sponsor's submission.

Another key element of informed consent is that participants be told of “appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.”³⁹ Participating patients would likely want to know that Copaxone® had already been shown to be clinically effective, and they would want to know what alternatives are available if they choose not to participate. Copaxone® became licensed in Canada during this study, and was available across the Canadian border in the US before the trial began. Thirty-four patients participated in Canada, and about 56% of them entered the study after Copaxone® became approved. There is documentation that two of the three Canadian sites updated their informed consent forms, but one center (Carter 50, Dr. Rice) did not. Further, there is no evidence thus far that subjects who had enrolled prior to Copaxone®’s approval in Canada executed new, updated informed consent forms after the drug’s approval there.

The FDA must refuse to grant an NDA application if the applicant has not complied with its regulations concerning informed consent.⁴⁰ No informed consent form used in this study gave a clear explanation of the study’s true purpose, which was to obtain MRI data on Copaxone®. Most were inadequate in describing alternatives, especially the availability of the drug in the US and other countries. This would have been especially valuable information to Canadian patients, some of whom might have elected to obtain the Copaxone in the US, or, as of September, 1997, in their own country.⁴¹

In our internal discussions of the ethical aspects of 9003, some have argued that MRI studies are necessary in MS trials, even where clinical efficacy is established. I agree that MRI is the “gold standard” in monitoring the disease in practice and in drug trials, as section 3 above makes clear. I have more trouble accepting the argument that MRI studies are needed where there is already clinical, logical, and some MRI data showing the same result as 9003. Regardless which point of view one adopts, there must be a balance between necessity of the research and the informed consent, which represent the potentially conflicting desires of the researcher and the rights of the patient, respectively. If there is an argument that the research may not really be necessary, then the researchers must be especially clear as to the purpose, and the Division should hold the sponsor to the highest standards with respect to its informed consent. Here, I believe the necessity was marginal at best, and sponsor failed to counterbalance this weak necessity by making sure the investigators gave complete and accurate informed consents.

³⁹ 21 CFR §50.25(4)

⁴⁰ 21 CFR §314.125(16) “Refusal to approve an application” (16) refers to informed consent, the requirements of which are located at 21 CFR §50.20, 50.25 & 50.27. The Canadian requirements are in the NSERC Ethical Conduct document cited above.

⁴¹ For studies performed abroad and not under an IND, regulation 21 CFR 312.120 provides that either the foreign country’s informed consent regulations or the Declaration of Helsinki must be followed, whichever provides the greater protection for the research subjects. Canada has informed consent requirements that have the same requirements as those spelled out in 21 CFR §50.25. Article 2.1C(iv), “Whenever possible and appropriate, the subjects will be provided with additional pertinent information after participation...”, Article 2.4D, “...will be given continuing and meaningful opportunity for deciding whether or not to continue to participate;” and Table 1, “1. An assurance that new information will be provided...whenever such information is relevant to a subject’s decision to continue or withdraw from participation.” (emphasis added)

In summary, the objective of 9003 was ethically flawed in that it recruited patients to participate in a study that was not necessary. From a regulatory standpoint, the protocol violated the requirements of informed consent that are required for NDA approval, and must be refused pursuant to 21 CFR §314.125(16), §50.20, §50.25, and §50.27 if conducted under an IND or under 21 CFR §312.120 and the Canadian informed consent regulations if not conducted under an IND. [Addendum: This study was not conducted under an IND, according to a review of our files and according to Teva (Scott Grossman, PhD.)]

8.2 Comments on Protocol Amendments

Initially patients who had previously participated in an Oral Myelin Trial were excluded from the 9003, but the exclusion was later amended. The amendment states that the reason for letting patients who participated in the Oral Myelin Trial participate in 9003 is because it "showed no clinical efficacy."⁴² This is a design flaw, in that the possibility of a synergistic effect between oral myelin and Copaxone® cannot be excluded. If any patients were admitted to 9003 who had received oral myelin, the possibility of a confounding variable was introduced. Data as to which patients, if any, received oral myelin, was not provided in this submission.

Besides the amendment discussed above (regarding oral myelin), there were amendments eliminating a definite amount of intra- and inter-observer reliability and for allowing the use IV steroids in the 6 months prior to entry for acute MS exacerbations.

Prior studies have shown that variability on MRI lesion counts in MS studies is at least in the 6% range. The amendment which eliminated a specific level of reliability and the elimination of the requirement that observers agree on every scan raises questions as to how reliable the lesion counts are in this investigation, especially in view of the fact that the scans were done on 29 different MRI scanners (discussed below). An attempt to show that they actually succeeded in maintaining a specified degree of reliability in their measurements or some quantification of it (e.g. a correlation coefficient comparing observers with themselves and with each other), would have been helpful. On the other hand, the result in this study is so highly statistically significant; any variability issue is probably only an academic point of little practical concern.

With respect to the use of IV steroids for exacerbations, it would not be ethical to deprive patients of this standard therapy. It was permissible during the trial to give IV steroids (1000 mg/day IV methylprednisolone for three days) for definite acute MS exacerbations. It would also have been impractical to bar an MS patient from participating (assuming the trial were a reasonable thing to do in the first place) because she had received IV steroids in the past 6 months, since this is a study of RR-MS.

Despite the necessity of allowing their use in and MS trial, IV steroids are known to affect the MRI. Acute enhancement has been reported to resolve in 96% of lesions following IV steroids.⁴³ Barkhof et al reported that high dose methylprednisolone treatment reduced enhancement as well as duration and severity of clinical relapses

⁴² Protocol Amendment No. 4, 1 March, 1998

⁴³ Müller DH, Thompson AJ, Morrissey SP et al, High dose steroids in acute relapse of multiple sclerosis: MRI evidence for possible mechanism of therapeutic effect. *J Neurol Neurosurg Psychiatry* 55(Supp 6):450-453, 1992.

temporarily, with 9.7 weeks being the average.⁴⁴ One way to mitigate this potentially confounding factor was the exclusion of patients who had received steroid treatment in the 30 days prior to the screening MRI. This is one approach used by sponsor.

Since the effects of IV steroids last more than 30 days, and average 9.7 weeks (68 days), we at least need to know that the use of IV steroids was balanced between the drug and placebo groups. IV steroids were used both in violation of the protocol and in accordance with it. Each type of steroid use will be discussed below.

Twenty-seven patients received steroids in violation of the protocol during the study (16 in the Copaxone® group and 11 in the placebo group). It was within the protocol to give steroids only for definite MS exacerbations. Violations, therefore, included lack of a documented MS exacerbation by the patient's study-neurologist, and involved high dose (1000 mg methylprednisolone IV for three days. More commonly, oral steroids were given for allergic symptoms, such as urticaria. Other violations included using doses in excess of 1000 mg methylprednisolone IV for 3 days, unusual routes of administration (IM, intrathecal), or indications other than documented acute MS exacerbations.

As a rough comparison, 27 courses of some kind of steroid treatment (in violation of the protocol) were given to patients in the Copaxone® group vs. 29 in the placebo group. With respect to high dose IV steroids, the Copaxone® group received 13 courses compared with 17 in the placebo group. Two patients in the placebo group received repeated doses; one of the placebo patients received 7 courses of IV methylprednisolone, and another had 2 courses of IV steroids, plus 13 days of IM, plus 3 intrathecal injections. The Copaxone® group, having received fewer courses (in violation of the protocol) than the placebo group, are not likely to have had the primary endpoint results inadvertently biased in their favor.

Although not violations of the protocol, high-dose (1000 mg IV daily for 3 days) methylprednisolone was given on one or more occasions to 79 patients in the trial for a total of 114 acute MS relapses. Most of the 114 courses of high dose steroids (1000 mg/day IV methylprednisolone daily for 3 days) were given to the placebo group, which received 68/114 courses of steroids for acute relapses compared to 46/114 steroid treatments in the Copaxone® group. (This is consistent with the previous studies that show Copaxone®-treated patients have fewer relapses than placebo-treated patients.) Thus, the potentially confounding effect of IV steroids would bias the results, if at all, away from the Copaxone®-treated group.

Three patients were marginally compliant with the study medication, two of whom (#'s 3410 and 5501) were in the Copaxone® group. Each of the marginally-compliant patients took the study drug about 40% of the time. Because non-compliance with Copaxone® would tend to bias the results against finding it to be effective, this protocol violation will not be considered further.

Another important protocol violation involved missed MRI scans. Twenty seven patients missed at least some scans and the range was from 1 to 7 with the average being 3.8.

⁴⁴ Barkhof F, Tas MW, Frequin ST et al, Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis. *Neuroradiology* 36:382-387, 1994.

The LOCF imputation method for missing data was used, and the results were significant regardless whether the data were analyzed using LOCF or "As Is."

8.3 Comments on the primary endpoint (total number of T1 Gd-enhancing lesions

Patients in the Copaxone® group had cumulatively fewer T1 Gd-enhancing lesions at the end of the 9-month double-blind period than those in the placebo group. Among those 213 patients who were evaluable at the end of the 9-month double-blind phase, the mean cumulative total of T1 Gd-enhancing lesions was 36.4 (SD 54.7) for the placebo group and 20.8 (SD 31.4) for the Copaxone®-treated patients. The medians were 17 and 11 for the placebo and Copaxone® groups, respectively.

Biostatistics has reviewed sponsor's results and analysis, and they will report their findings separately. Because the data were not normally distributed, a parametric method such as was used here, was inappropriate. The Data Analysis Plan called for using either rank or log-transformed data, i.e., nonparametric approaches better suited to the highly skewed data.

Biostatistics also finds that the use of adjusted means, which was done with every endpoint, was also inappropriate. As Dr. Yan points out in her review, "An adjusted mean is an estimate of the mean for the parameter of interest by using a specific model. It does not mean that the underlying model is a correct model or the predicted mean is close to the true mean. The adjusted means presented in the proposed labeling were from invalid models and are therefore, not appropriate and misleading. For example, in the model of parametric ANCOVA for the primary efficacy endpoint, the normal assumption was severely violated and alternative methods became necessary. In addition to the violation of the normal assumption, covariates other than those specified in the protocol were added to the model. Therefore, in this reviewer's opinion, all adjusted means should be removed from the labeling."

By applying log and rank transformations to the data and by ignoring adjusted means, biostatistics still finds that Protocol 9003 provided sufficient evidence that Copaxone-treated patients had fewer T1 Gd-enhancing lesions on MRI than placebo-treated patients during the trial. (For the log-transformed data, a p-value of 0.0044 in favor of the Copaxone group was obtained; for the rank-transformed data, p=0.0030.)

This primary endpoint result of Protocol 9003 is not surprising. As stated above, Copaxone® had already been shown to reduce the frequency of relapses, and the MRI finding during a relapse is a Gd-enhancing lesion on a T1-weighted scan. Furthermore, MRI data collected during sponsor's 01-9001 trial showed that Copaxone® had an effect on MRI that parallels its effects on the clinical relapse rate.⁴⁵

⁴⁵ Johnson KP, Bornstein MB, "Treatment of Multiple Sclerosis with Copolymer I," in Goodkin DE and Rudick RA, eds., Multiple Sclerosis: Advances in Clinical Trial Design, Treatment and Future Perspectives, Springer, 1996, p. 307. (Results later published in full in: Ge Y, Grossman RI, Udupa JK et al. Glatiramer acetate (Copaxone) treatment in relapsing-remitting MS: quantitative MR assessment. Neurology 54:813-17, 2000.

8.4 Comments on secondary endpoints

There are six secondary endpoints specified in the protocol:

1. The "proportion of T1 Gd-enhancing lesion-free patients" was not an endpoint in original protocol, but sponsor states it is the complementary value of the proportion of patients with Gd-enhancing lesions (the endpoint defined in the protocol).⁴⁶ Presumably sponsor chose to rename this endpoint to enable them to promote Copaxone® as a drug that increased the proportion of lesion-free patients over placebo. Unfortunately, there was no significant difference between drug and placebo groups at the end of the 9-month double blind phase. Sponsor would like to view the data by trimesters and state that, in the last 3 months of the placebo-controlled phase the difference between the drug and placebo groups became significant. Because this is a post-hoc approach (there were no plans a priori to break the placebo-controlled phase into trimesters), such observations cannot be accepted in the labeling, especially for a secondary endpoint. There was no significant difference between the drug and placebo groups on this MRI endpoint. Of the 43 patients who were lesion-free at 9 months, 21 were in the Copaxone® group and 22 in the placebo group.
2. With respect to the volume of Gd-enhanced lesions on T1-weighted images, sponsor chooses to report only the change from baseline to month 9. The protocol, however, specifies for all volumetric endpoints a rank-transformed Repeated Measures Analysis (RMA). Sponsor's p-value (RMA, rank; see the January, 2000 report) is $p=0.0098$. In the July, 2000 Final Report, however, sponsor gives the result only for baseline to 9 month and used a parametric method inappropriate to the highly skewed data. The original (January 2000) RMA rank should be the result reported. The Division's biostatistician obtained a result close to that, $p=0.0105$, RMA rank.
3. The total number of new Gd-enhanced lesions in T1-weighted images was not normally distributed and therefore the parametric method used by sponsor was not appropriate. The protocol specified that a log- or rank-transformation would be used. Since the volumetric analyses involve changes in volumes that can be negative, a log-transform cannot be used, therefore the only method that could be applied consistently across *all* endpoints (and still be compliant with the protocol) would be a rank transformation. (Biostatistics found $p=0.0154$ for rank-transformed data; for log-transformed data it was 0.0048)
4. The comments made with respect to the total number of new lesions in T2-weighted images are similar to those made with respect to T1 (see 3., above). A rank-transformed approach will give a higher p-value than the 0.0029 reported by sponsor, who used a parametric approach. Again, the latter approach is unsuited to these data, which are highly skewed. (Biostatistics obtained a $p=0.0769$ for rank-transformed data and 0.0073 for log-transformed data.)

⁴⁶ Final Report of Protocol 9003, July 2000, p. 25).

5. The comments made with respect to the other volumetric endpoint (see 2., above) apply to the volume of lesions in T2-weighted images. Sponsor's protocol called for a rank-transformed RMA approach, but sponsor reports only a comparison of baseline to month 9 and used a parametric method. Sponsor's RMA rank p-value (in the January, 2000 report) is 0.0245. Our biostatistician obtained a similar value, 0.0259.
6. The volume of hypointense lesions on pre-Gd T1 images was not significant by RMA rank at the p-value calculated by sponsor (see January 2000 report), p=.8974. Our biostatistician obtained a similar value, 0.8916.

Summarizing Biostatistic's results is Table 3, taken from their review:

Table 3. Summary of Efficacy Analysis from Secondary Measures

Secondary Measure	Parametric Model (p-value from normal test)	Log-transformed	Rank-transformed
Proportion	N.S. ¹	N.A. ²	N.A. ²
T1 lesion volume	0.0340 (0.0001)	N.A.	0.0105
T2 lesion volume	0.7592 (0.0001)	N.A.	0.0259
# of new T1 lesions	0.0016 (0.0001)	0.0048	0.0154
# of new T2 lesions	0.0197 (0.0001)	0.0073	0.0769
T1 Hypo volume	0.9386 (0.0001)	N.A.	0.8916

1. N.S.: not significant

2. N.A.: not applicable

Note that, with a Bonferroni adjustment for 6 secondary endpoints, a required significance level of 0.0083 (0.05 divided by 6) is obtained. If one uses the log-transformed data, then 2 of the 6 secondary endpoints reach statistical significance, i.e., the number of new T1 and and the number of new T2 lesions. If one uses the rank-transformed data, however, none of the secondary endpoints are significant. With the volumetric analyses, a log-transformation cannot be used, because the data include negative numbers. One could therefore argue that the only consistent approach would be to use rank-transformed data for each endpoint; but this would mean no secondary endpoint was significant.

8.5 Comments on Sponsor's Conclusions Regarding Clinical Results

The protocol does not list neurological assesment even as a secondary outcome variable. On page 18 of the protocol (July 17, 1996), objects 3.1.1 (primary) and 3.1.2 (secondary) are all MRI parameters. The subsequent paragraph of the protocol, 3.2, states that, after the double-blinded phase, all patients will be rolled over into the open label treatment for an additional 9 months, and that exploratory data assesment will attempt to evaluate...the correlation between MRI activity and clinical measures of disease.⁴⁷ What use of the neurological data, if any, appears to be aimed at exploring the relationship between MRI parameters and clinical ones.⁴⁸

⁴⁷ Protocol 9003, 17 July 1996, 3. Objectives, et seq at p. 18.

⁴⁸ Protocol 9003, July 17, 1996, data evaluation, p 55

As an issue that is merely “exploratory” and only being done during the open-label phase, any neurological conclusions should be limited to the count of relapses. This figure was known with confidence, since the protocol required that the study neurologist, who was blinded to the study drug, decide whether the patient was truly having a relapse. High dose steroids for 3 days were then given. Any other clinical conclusion was not obtained pursuant to the controlled part of the protocol and cannot, therefore, be a proper basis for labeling changes.

8.6 Overall Comments and Conclusion on Protocol 9003

The results of 9003 are fruits of a study tainted by patient consent that was not properly informed. The clearest example occurred in Canada where patients were enrolled during the time Copaxone® was available across the border in the U.S. and, about 3 months after the first patients were enrolled there, in Canada itself. Patients must be told of alternative treatments according to both US and Canadian regulations cited above.

The true purpose of the research, “*to determine....the effect of copolymer-1 on MRI measured disease activity*”⁴⁹ was never provided to prospective study participants in so many words. The purpose was instead obfuscated by the words, “to determine the effect of a drug Copaxone.....*on disease activity in the brain....*,”⁵⁰ and the fact the drug’s clinical efficacy was “already proven” was not uniformly or clearly disclosed. Patients must be told the purpose of the research according to both US and Canadian regulations cited above.

Had the consent been obtained from fully informed patients and properly documented according to 21 CFR 50.27 (the documentation of informed consent), the sponsor might have overcome the necessity issue. As stated above, there is reason to question the ethical necessity of Protocol 9003. Absent a strong showing of necessity and coupled with significant gaps in the informed consent, this reviewer recommends the sponsor be strongly reminded of the legal requirements for informed consent. **Whether the more drastic action of excluding some patients’ data (e.g., the Canadians’) from the analysis, or even barring any reference to MRI Protocol 9003 in the labeling has been discussed internally in the Division. The consensus is that the behavior was not egregious, pervasive, or reckless enough to warrant the more drastic remedies.**

In any discussion about preventing a sponsor from harvesting the fruits of an ethically-tainted protocol, one needs to keep in mind the potential that the Agency’s action may have unwanted effects on the public. However, the medical community relies more on medical literature than on labeling as a source of new medical knowledge; labeling issues matter to a sponsor in large part because they form the basis for promotional claims. Therefore, depriving a sponsor of the fruits of an ethically-flawed study harms the sponsor economically; the medical literature and its readers are unlikely to be harmed.

⁴⁹ Id. p. 18 (emphasis added)

⁵⁰ See consent documents, Vol. 34.4 of sponsor’s submission (emphasis added)

9. Proposed Labeling Changes: Background

There are several types of labeling changes sought by sponsor:

- Additions to the label based on the primary endpoint 9003 (A major addition)
- []
- Additions to the label due to adverse event reporting
- []

9.1 Administrative History

The NDA for COPAXONE® was originally submitted on June 13th, 1995 and approved on December 20th, 1996. On August 4th, 1999, the sponsor filed a supplemental NDA, reference number SLR-015 to make changes to labeling sections. The sections sponsor sought to change include:

- CLINICAL PHARMACOLOGY (Mechanism of Action, Pharmacokinetics, and Clinical Trials),
- INDICATIONS AND USAGE,
- PRECAUTIONS (Considerations Regarding the Use of a Product Capable of Modifying the Immune Responses, Drug Interactions, and Carcinogenesis, Mutagenesis, Impairment of Fertility), and
- ADVERSE REACTIONS (Chest Pain).

(There were also minor editorial changes sought throughout the labeling.)

The supplemental NDA, reference number SLR-015, consists of 8 volumes containing 23 Attachments. Attachments 1 and 2 are the new (proposed) and current labels, respectively, with annotations. Attachments 3-8 provided a basis for changes to the CLINICAL PHARMACOLOGY section. Attachment 9-14 provide a basis for what appears to be a *post-hoc* analysis of data from the second COPAXONE® trial and its extension (01=9001/9001E).

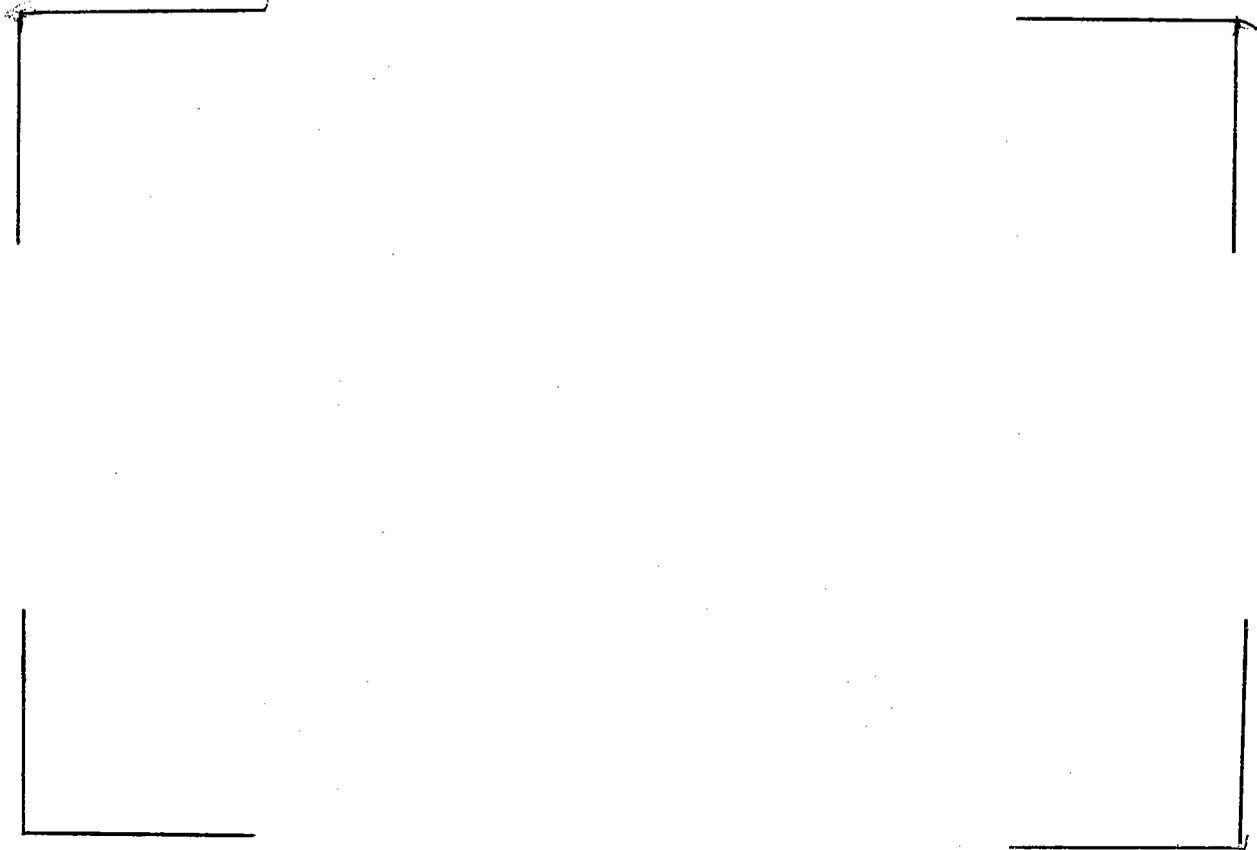
Attachment 15 is protocol 9003, double blind phase, describing the MRI study and its results. (The long-term MRI open-label data was submitted in April, 2000.) The remaining attachments address issues affecting other labeling sections listed above.

9.2 Applicable Administrative Regulations and Guidelines

21 CFR §§ 314.70(b)(3)(i), 314.71, and 314.50 provide the mandatory legal requirements for labeling supplements and other changes to approved applications to market a new drug (NDAs) under § 505 of the Federal Food, Drug, and Cosmetic Act. 21 CFR § 314.125 provides the mandatory bases for refusal to approve an NDA, and the required informed consent regulations are 21 CFR §§ 50.20 through 50.27. For foreign studies not done under an IND, see footnote 41, above.

25 page(s) of draft
labeling has been
removed from this
portion of the review.

Medical Review



Appendix

TEVA COPAXONE 9003 TRIAL

STAFF TRAINING

The STAFF TRAINING staff has been trained for three months to improve the intra- and inter-observer reproducibility for both quantitative measurements of brain MRI lesion load (action: technicians) and lesion counting (action: neuroradiologists).

This is a protocol designed to provide you with data coming from brain MRI images obtained with the same acquisition parameters as the ones which will be acquired for the Copaxone protocol.

Patient studied 10

MPI sequences: T2-weighted, pre-Gad T 1-weighted, post-Gad T 1-weighted

Materials: hardcopies + electronic data stored on DAT tape

⁵⁹ Ibrahim S, NDA Review, Id. at page 6.

- The lesions will be marked on the hardcopies (using transparent sheets as a mask) by the two neuroradiologists by consensual agreement. For each sequence the number of hyperintense lesions (T2WI), of hypointense lesions (pre-Gad T1WI) and of enhancing lesions (post-Gad T1WI) will be computed

- Lesion volume assessment will be done for each kind of image by the four technicians, using a local thresholding technique for lesion segmentation and using the marked hardcopies as a reference.

The whole above described procedure will be repeated after 20 days of interval. Previously marked transparent sheets will be preliminarily removed and new, blank ones will be stuck [sic] to the hardcopies.

Therefore you will be able to assess the intra-observer reproducibility for lesion counting (inter-observer reproducibility is not requested because for the study the analysis will be done by consensual agreement) and both the intra- and the inter-observer *reproducibility* for lesion load assessment.

Comments Summarized

1. The primary endpoint of 9003 achieved statistical significance. In view of the fact that the data are highly skewed and a parametric model is inappropriate, a p-value of 0.0030 (rank transformed) should be used.
2. The secondary endpoints of 9003 as defined by the protocol should be analyzed using rank-transformed data, for the same reason given in comment 1, above.
3. Using rank-transformed data and adjusting for multiplicity, none of the secondary endpoints of 9003 reach statistical significance.

4.

5.

6. With respect to the ethical problems of 9003, this reviewer noted sponsor did not comply with informed consent regulations. Specifically, the Division has not been provided documentation, despite oral and written requests, that any patients who had been enrolled prior to September 1997 (the date Copaxone was approved in Canada) executed new, revised consent forms. Furthermore, in Center 50, the forms were never revised to reflect the approval of the drug in Canada. In addition, the trial was permitted to continue despite the results of the second interim analysis. Lastly, sponsor may have falsely assured the Division (on January 11, 2001) upon repeated oral and written questioning, that the Canadian subjects enrolled before Copaxone's approval re-

executed new, revised informed consent documents, and that documentation of this was sent. The documents received, however, merely offer excuses why Center 50 did not revise its consent, but provide no response whatsoever to the question of whether those enrolled before September 1997 re-executed new, revised forms (at Centers 51 and 52). If this last "assurance" was a deliberate attempt to mislead the Division, it could be a criminal offense according to 18 USC 1001. Failure to comply with informed consent is grounds for denial of approval of an application according to 21 CFR 314.125(16) and 312.120. **Sponsor should be strongly warned of the seriousness of CDER's mission with respect to protecting the rights of human research subjects, and an investigation of the 3 Canadian centers (50, 51 & 52—all in []) should be conducted to review any and all consent forms the subjects may have signed.**

Recommendation

I recommend an approvable letter be sent with the label I submitted as a separate document, provided sponsor addresses the ethical issues of comment 6, above. Please convey my comments 1-6 above to the sponsor.

Gerald Tremblay, M.D.
Medical Reviewer

John Feeney, MD _____
Team Leader

R. Katz, M.D. _____
Division Director

cc:
HFD-120

MEMORANDUM

NDA 20-622/SLR-015 Copaxone (Glatiramer Acetate for Injection)

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Labeling Supplement

DATE: January 12, 2001

Copaxone was approved for marketing in the US for the treatment of relapsing-remitting multiple sclerosis (MS) on December 20, 1996. The sponsor has now submitted a labeling supplement, incorporating several different pieces of evidence. First, the sponsor has performed a placebo-controlled trial investigating the effects of Copaxone on MRI findings in patients with relapsing-remitting MS (Study 9003). The sponsor wishes to describe the results of this trial in labeling. []



The primary clinical review of this supplement has been performed by Dr. Gerald Tremblay. Dr. Sharon Yao has performed the statistical review.

The sponsor has also provided for changes to numerous other sections of labeling, to include the Pharmacokinetics subsection. Dr. Hong Zhao has reviewed these changes. Changes pertaining to preclinical studies have been reviewed by Dr. Roney.

Study 9003

This was a randomized, double-blind, placebo-controlled, parallel-group trial investigating the effects of Copaxone on MRI parameters in patients with relapsing-remitting MS. Patients were randomized to Copaxone or placebo and followed on double-blind treatment for 9 months. During this time, MRIs were planned monthly for all patients. The primary protocol-specified outcome variable was the cumulative number of T1 gadolinium (Gd) enhancing lesions for each patient during the course of the trial.

A total of 239 patients were randomized: 119 to Copaxone and 120 to placebo.

The study was not performed under the US IND. The study was conducted at 29 centers in Belgium, France, Germany, Holland, Italy, UK, and Canada. The first patient was enrolled on March 12, 1997 and the last observation under double-blind treatment was taken on August 21, 1998.

Inclusion/Exclusion criteria required patients to demonstrate at least one Gd-enhancing lesion on a screening MRI scan.

By the protocol-specified primary analysis, Dr. Yan has confirmed the sponsor's conclusion that patients randomized to Copaxone performed better than patients randomized to placebo.

There were 6 protocol-specified secondary outcome variables. The sponsor and Dr. Yan emphasize different results for these secondary analyses; the different results arise in large part from different assumptions about the normality of the data. The reviews of Dr. Tremblay and Dr. Yan provide the details of these analyses.

The sponsor and the division, then, agree that Study 9003 provides evidence for an effect of Copaxone on T1 Gd-enhancing lesions in MS patients.

Adequacy of Informed Consent During the Conduct of Study 9003

Background: The use of placebos in clinical trials can be problematic. Because Copaxone was approved for marketing in the US prior to the enrollment of the first patient in Study 9003, this application was scrutinized more than most during Dr. Tremblay's review, to ensure the adequacy of informed consent.

Copaxone was approved in the US on the basis of 2 adequate and well-controlled clinical studies with clinical outcomes. These results had also been publicly reviewed by the PCNS Advisory Committee and deemed adequate to support the conclusion that Copaxone provided clinical benefit to the sort of patient enrolled in Study 9003. I acknowledge that some communities would require a higher standard of evidence before concluding that Copaxone was effective in MS. Further studies might have been required to obtain regulatory approval in countries other than the US. However, as the review of this application was undertaken, we recognized that, in 1997, a placebo-controlled trial of Copaxone might have met resistance during the IRB review process in the US. For that reason, especially, we pursued affirmation that the rights of patients in other countries were protected during the conduct of this trial, as evidenced by the adequacy of the standard informed consent document at each study site.

Non-Canadian Sites: During the conduct of Study 9003, Copaxone was not marketed in any of these sites. I do not believe there are any glaring deficiencies in the IC documents provided for those sites.

Canadian Sites: There were 3 sites in Canada:

5000	10 patients
5100	12 patients
5200	12 patients

During the conduct of Study 9003, in September, 1997, Copaxone was licensed for marketing in Canada. The last observation under double-blind treatment occurred on August 21, 1998. Therefore, patients, already enrolled as of September, 1997, needed to have informed consent re-executed reflecting the new information. The other newly-enrolling patients in Canada needed to be informed, prior to study entry, that Copaxone was licensed. Thirty-four patients participated in Canada; more than half entered after Copaxone's licensing there.

Center 5000 never incorporated this information (licensed for marketing) into the standard written IC document. The patients may have been verbally informed, but no written record was maintained. Therefore, neither ongoing nor newly-enrolling patients at this site (n=10) could have executed adequate written informed consent.

Centers 5100 and 5200 did update the standard IC document, but it is not yet clear if the revised informed consent was executed for both the newly-enrolling and the already-enrolled patients.

Interim Analyses: Two interim analyses were planned. The second was performed when the first 160 patients completed the double-blind phase. The p-value reached the predefined level of significance. On June 14, 1998, this result was discussed by the External Advisory Committee, but a decision was made not to stop the trial. As noted above, the last observation under double-blind treatment occurred 2 months later on August 21, 1998.

In Canada, because Copaxone had been licensed 9 months earlier based on clinical data, I personally believe the results of this second interim analysis should have immediately led to cessation of double-blind treatment for all patients in Canada. At least, written consent should have been updated with this information.

In all of Canada, roughly 5 patients continued on double-blind treatment for a month or longer after the second interim analysis. Only 2/5 had been randomized to placebo. One of these 2 remained on placebo for 2 months after the June 14 meeting. [This last patient, Pt 5212, enrolled at Center 5200 after Copaxone licensing in Canada, but apparently with adequate written informed consent. The patient continued to receive placebo for 9 months; 2 of these 9 months were after the June 14 meeting.]

Conclusions

Quantitatively, the problem of adequate informed consent in Study 9003 may appear small. Only a fraction of the patients enrolled were in Canada. Not all of these patients were affected by the problem.

Nevertheless, given the worldwide drug development plan for Copaxone, the burden was on the sponsor to ensure that every single patient executed written informed consent for the entire duration of the trial. The sponsor failed to do this.

The demonstration of efficacy, the regulatory approval, and the actual accessibility of a drug product are not usually concurrent events. Ideally they would be. In the world of Patient 5212 (discussed above), the sequence of events was: the demonstration of Copaxone's efficacy in placebo-controlled trials, leading to regulatory approval in Canada (September 1997), followed by personal involvement in further placebo-controlled study (7 months) which again supported efficacy (June 14, 1998 interim analysis), followed by personal involvement in placebo-controlled study for 2 more months. Personally, at this time, it does not appear to me that this sequence of events was in the best interest of Patient 5212. At the least, updated written informed consent should have been executed immediately after the interim analysis. Perhaps the patient should have been crossed over from placebo to active drug (Copaxone) immediately. Adequate written informed consent was lacking for other patients in Canada.

In summary, I have not been convinced that the rights of all subjects were adequately protected.

Recommendation

CFR 314.125 states, "The Food and Drug Administration will refuse to approve the application...if...(b)(16) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected."

I cannot tell from the written records collected during the conduct of the trial whether the rights of human subjects were protected or not. Therefore, it becomes a judgment call. My judgment (and I recognize that this may be debatable) is that they were not.

Therefore, approval should not be granted for this application. The sponsor should be asked to submit components of this application unrelated to Study 9003 under a different application. DSI should be incorporated into further discussions about these issues. For-cause inspections of the Canadian sites should be requested.

cc: NDA 20-622
Katz/Feeney/Tremblay/Wheelous

/s/

John Feeney
1/17/01 12:07:26 PM
MEDICAL OFFICER

MEMORANDUM

NDA 20-622/SLR-015 Copaxone (Glatiramer Acetate for Injection)

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Labeling Supplement

DATE: June 1, 2001

Copaxone was approved for marketing in the US for the treatment of relapsing-remitting multiple sclerosis (MS) on December 20, 1996. In a recent labeling supplement, the sponsor proposed describing the results of a new study, Study 9003, in labeling. Study 9003 investigated the effects of Copaxone on MRI findings in patients with relapsing-remitting MS. In an action letter dated January 19, 2001, DNDP requested more detailed information about informed consent during the conduct of that trial.

Study 9003

This was a randomized, double-blind, placebo-controlled, parallel-group trial investigating the effects of Copaxone on MRI parameters in patients with relapsing-remitting MS. Patients were randomized to Copaxone or placebo and followed on double-blind treatment for 9 months. During this time, MRIs were planned monthly for all patients. The primary protocol-specified outcome variable was the cumulative number of T1 gadolinium (Gd) enhancing lesions for each patient during the course of the trial. A total of 239 patients were randomized: 119 to Copaxone and 120 to placebo.

The study was conducted at 29 centers in Belgium, France, Germany, Holland, Italy, UK, and Canada. The first patient was enrolled on March 12, 1997 and the last observation under double-blind treatment was taken on August 21, 1998. During the conduct of Study 9003, Copaxone was not marketed in any of the non-Canadian sites. However, during the conduct of Study 9003, in September, 1997, Copaxone was licensed for marketing in Canada.

In our letter of January, 2001, we asked the sponsor to outline in detail the efforts made to provide adequate written informed consent at all Canadian sites, specifically incorporating information about Copaxone's approval in Canada.

Current Submission

The sponsor has outlined efforts to obtain adequate written informed consent in Canada.

There were 3 sites in Canada, each enrolling about 10 patients. Once Copaxone was approved for marketing in Canada and was available, the sponsor communicated with the 3 sites about this new development. Two of the sites updated the informed consent document. One site did not update the informed consent document. The investigator at that site states that patients were verbally made aware of Copaxone's recent approval.

Conclusions

Prior to the conduct of Study 9003, Copaxone had been shown to reduce the frequency of attacks of MS in placebo-controlled trials. During the conduct of Study 9003, regulatory authorities in Canada acknowledged this fact and granted marketing approval for Copaxone.

Attacks of MS can range from mild to severe, the most severe including optic neuritis and transverse myelitis. Given that attacks of MS can be serious and given that Copaxone was approved in Canada to decrease attacks of MS, the decision to continue enrolling patients in placebo-controlled trials of Copaxone was not a trivial one. On the contrary, I believe that the burden of responsibility on the sponsor and investigator increased at the time that Copaxone was approved for marketing in Canada.

Those involved in the conduct of Study 9003 made a measured decision to continue exposing patients to placebo. They should have recognized the added importance of obtaining adequate written informed consent from each and every patient exposed to placebo beyond Copaxone's approval date. In the current submission, the sponsor has made it clear that sponsor and investigator alike failed to meet the added responsibility.

Every patient has a right to adequate written informed consent. Even more so during the conduct of placebo-controlled trials of already approved drug products.

CFR 314.125 states, "The Food and Drug Administration will refuse to approve the application...if...(b)(16) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in part 56 of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected."

Because the right to written informed consent was not adequately protected during Study 9003, I believe this labeling supplement should not be approved.

Recommendation

This labeling supplement should not be approved.

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

/s/

John Feeney
6/18/01 12:39:30 PM
MEDICAL OFFICER

MEMORANDUM

DATE: January 15, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-622/SLR-015

SUBJECT: Action Memo for NDA 20-622/SLR, for amendments to the labeling of Copaxone (glatiramer acetate)

On 8/4/99, Teva Pharmaceuticals, Inc., submitted SLR-015, a supplement to their approved NDA 20-622, for the use of Copaxone, currently approved for the reduction of frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS). The labeling supplement contained the results of Study 9003, a 9 month, randomized, double blind, placebo controlled, parallel group trial which utilized MRI as the primary outcome. Specifically, the total number of Gadolinium enhanced T1 lesions over the 9 months was the primary outcome, with several other MRI measures as secondary outcomes. Clinical measures were not proposed in the protocol.



☐ In addition, they want to include a description of the findings in Study 9003. Further, they want to change the Indication to read as follows:

☐ Copaxone is indicated for the management of relapsing-remitting multiple sclerosis by reducing the frequency of relapses. ☐

☐ This supplement has been reviewed by Dr. Gerald Tremblay, medical reviewer (review dated 1/19/01), Dr. Sharon Yan, statistician (review dated 1/12/00), Dr. Paul Roney, pharmacologist (review dated 11/27/00), Dr. Hong Zhao, Office of Clinical Pharmacology and Biopharmaceutics (reviews dated 5/2/00 and 12/13/00), and Dr. John Feeney, Neurology Team Leader (review dated 1/12/01). Both Drs. Feeney and Tremblay have expressed serious concerns about the ethics of Study 9003, for several reasons, and Dr. Feeney has recommended

that the application not be approved based on what he concludes are serious and significant ethical problems.

In this memo, I will very briefly review the relevant data for Study 9003, address the concerns raised by Drs. Tremblay and Feeney, and provide support for the Division's action on this supplement.

STUDY 9003

This study was performed in 25 centers in Europe and Canada. As described by Drs. Tremblay and Yan, a total of 239 patients were randomized (Copaxone 119, Placebo, 120). While the sponsor presented the results of an ANCOVA on the mean number of lesions (the protocol specified analysis), Dr. Yan noted that the data were not normally distributed, and therefore the protocol specified analysis was inappropriate. The protocol apparently stated that if this was the case, both log and rank transformed analyses would be performed. The results of the primary outcome, the Total Number of Gd+ lesions on MRI over 9 months were, according to Dr. Yan:

	Median	P-value (Log)	P-value (Rank)
Copaxone	11		
Placebo	17	0.004	0.003

The following table, taken from Dr. Yan's Table 3, (page 12) describes the results of the analyses of the protocol specified secondary outcomes, using the protocol specified analyses, given that the data, as for the primary measure, were not normally distributed (I cannot easily find in either the clinical or statistics review the actual estimates of the treatment effects for the specific measures):

	P-value (Log)	P-value (Rank)
Proportion of Pts With Gd+ Lesions	NA	NA
T1 Lesion Volume	NA	0.011
T2 Lesion Volume	NA	0.026
# of New T1 Lesions	0.005	0.015
# of New T2 Lesions	0.007	0.077
Volume of Hypointense T1 Lesions	NA	0.89

As noted above, Dr. Tremblay has raised several ethical issues with this study.

In particular, Dr. Tremblay has serious misgivings about the ethical conduct of the trial, because, in his view, it is a “logical inference” that the drug would have an effect on the MRI, a more sensitive measure than clinical outcomes, given that the drug has already been shown to have an effect on clinical outcomes. Given the logical inference that the drug must have an effect on the MRI, Dr. Tremblay has concluded that enrolling patients into a trial in which there is a 50% chance of receiving placebo is unethical.

I cannot agree that one could **know**, a priori, on the basis of logic, that Copaxone would have the effect that ultimately was seen on MRI in this study. While such a prediction would have been reasonable, of course, the exact nature and extent of the MRI changes seen were not a given, in my view. Although data continues to be generated relating drug effects to MRI outcomes in patients with RRMS, the evidence across various drug classes is not very robust, and does not provide, yet, in my view, assurance about the nature of MRI changes associated with treatments of varying types (Dr. Tremblay’s argument would be stronger, it seems to me, if the drug in question here was another beta-interferon). The information about Copaxone’s effect on MRI (at least in this trial) may very well provide additional useful information to the clinician contemplating treating a patient with this drug, especially given the relatively small (clinical) treatment effects seen in previous clinical trials. Although other trial designs could have been performed, only the design utilized here was capable of addressing the simple question of whether or not Copaxone treatment, by itself, is associated with MRI changes. In particular, active controlled trials, one example cited by Dr. Tremblay, are ordinarily not interpretable (if, as is usually the goal, no difference is detected between the treatments), and would be expected to give no useful information.

Further, while there is now a growing consensus among many MS experts that placebo monotherapy studies may be unethical in patients with RRMS who are eligible for treatment with one of the currently approved drugs, this consensus has only very recently been arrived at, and was not at all the case when this trial was done; indeed, many such trials were on-going at the time. In fact, even now, in the UK and elsewhere, it is my understanding that the view that such trials are unethical is not universally held.

Dr. Tremblay goes on to state that, given the dubious ethical status of the trial in the first place, the sponsor had the obligation to make as clear as possible to study participants, the purpose of the study in the Informed Consent document. I agree, although I disagree with Dr. Tremblay that the Informed Consent was importantly misleading. Apparently, the documents described the purpose of the study as determining the effect of Copaxone on disease activity in the brain. While I do agree that a more explicit statement about MRI might have been helpful, I think that the phrase “disease activity in the brain” reasonably

describes, in lay terms, what the primary purpose of the study was (after all, the patients also knew that they would be getting multiple MRI scans as well).

A critical, related issue relates to what information the patients received about the availability of Copaxone outside this trial. While the drug was approved in the US during the conduct of the trial, that was not the case for the locations in which the trial was performed. Both Drs. Tremblay and Feeney believe that (some) patients may have been inadequately informed about the availability of Copaxone outside the trial. If they had not been adequately informed, I would agree that there might be serious objections, on ethical grounds, to the trial as conducted.

Specifically, Copaxone became available in Canada during the conduct of this trial (it was not available in any of the other countries in which the trial was performed). A total of 34 patients were enrolled in 3 sites in Canada. According to Drs. Tremblay and Feeney, about 2/3 of the patients enrolled after the drug became available. The sponsor has provided evidence that 2 of the 3 Canadian sites did update their consent forms after the drug became available. Although at the time Dr. Tremblay wrote his review there had been no documentation that the consent form had been changed at the 3rd site (Dr. Rice, Principal Investigator), we have subsequently received a submission from the sponsor (dated 1/5/01) that includes a letter from Dr. Rice. In that letter, Dr. Rice acknowledges that, while the informed consent documents were not altered, he did inform all patients enrolled subsequent to the drug's availability that it was, in fact, available to them outside the trial. Importantly, as both Drs. Tremblay and Feeney point out, the application contains no information about whether or not patients already enrolled in the trial had been informed that the drug had become available. At a meeting held on 1/11/00 with the sponsor, I believe they informed us that all patients had been told that the drug had become available, but I do not believe that we have received an adequate answer to this question, and we should ask for more specific, detailed information on this point.

Dr. Feeney has raised another ethical question.

According to the protocol, 2 interim analyses were contemplated, and performed. The trial met its statistical endpoint on the second interim analysis, and, according to Dr. Feeney, the results were discussed at an External Advisory Committee meeting on June 14, 1998. Although the study was, by protocol, to be stopped at that point, the Committee decided that the trial should continue until the end, which was 2 months later, August 19, 1998. As Dr. Feeney describes, one patient remained on placebo for these 2 months. At the 1/11/00 meeting with the sponsor, we also asked them to justify this continued treatment. While the sponsor offered an explanation (one of the members of the Committee, Dr. Jerry Wolinsky, was at the 1/11/00 meeting, and offered that there had been extensive discussions on this point, but that it was decided to continue the study for various reasons), we should ask the sponsor again for specific, detailed

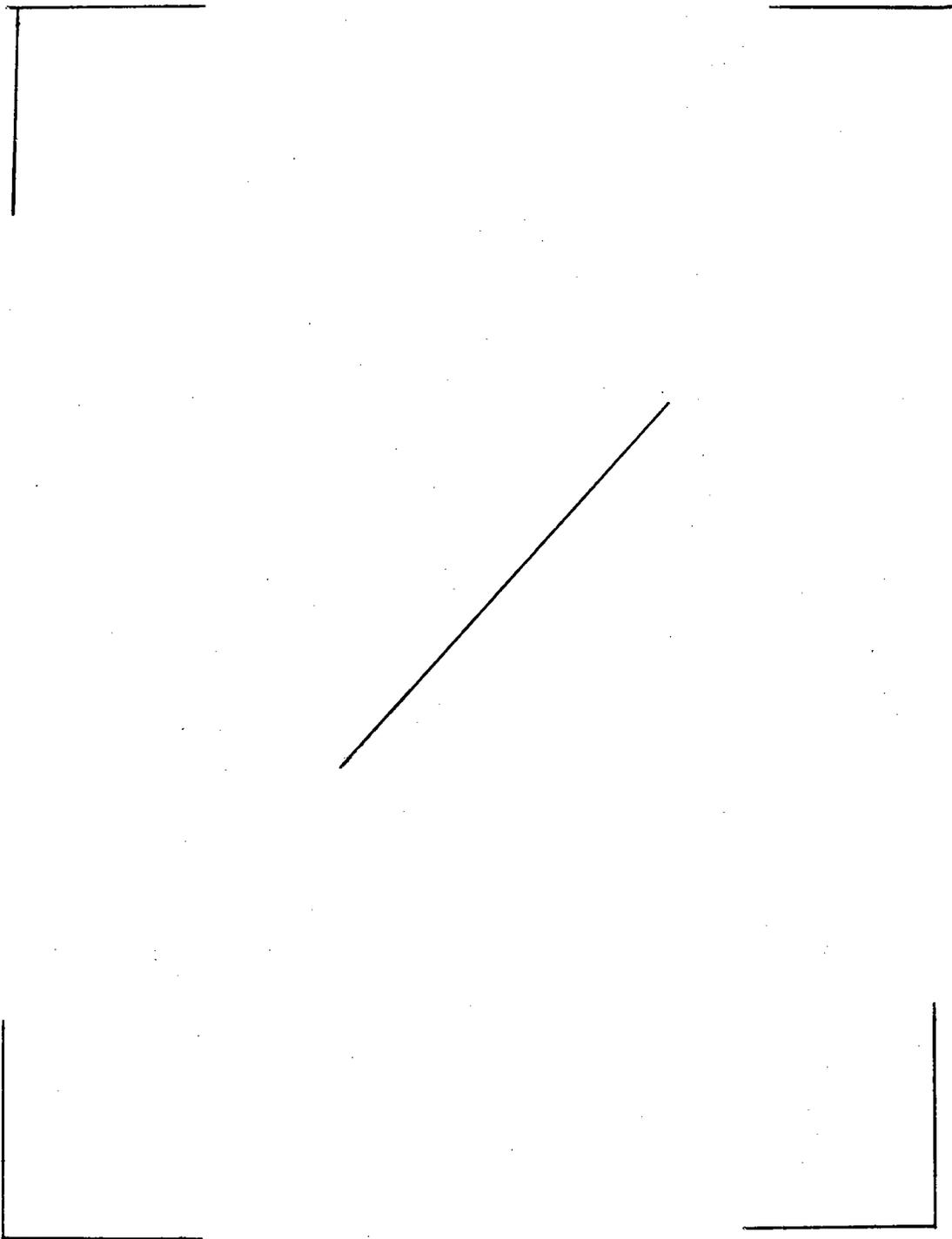
reasons for their decisions (e.g., minutes of the External Advisory Committee meeting). Dr. Feeney concludes that treating this patient for an extra 2 months constitutes a violation of 21 CFR 314.125 which states that the FDA will refuse to approve an NDA if, among other things, any investigation is not conducted in compliance with the Informed Consent regulations such that "...the rights or safety of human subjects were not adequately protected." (Dr. Tremblay cites this section of the regulations also).

Although there is additional data, noted above, that the sponsor should be asked to submit, I cannot agree, at this time, with Dr. Feeney that the continued treatment of this patient violated our regulations.

While we have not obtained legal or other expert input on this question, it seems to me that the sponsor (and/or the investigators) made a good faith effort to conduct the study, and administer informed consent, according to accepted ethical standards. There do seem to have been lapses (for example, Dr. Rice should have obtained **written** informed consent when Copaxone became available, and, according to Dr. Tremblay, the requirements in Canada are similar to those here), but in general, reasonable efforts seem to have been made. It is not uncommon, in my experience, that for any given patient in a given study, the informed consent obtained may not have been strictly adequate. I take Dr. Feeney's point that the single patient described above should have been informed of the results as soon as they became available, but I can imagine a number of reasons why the study could have been reasonably continued. For example, while I do not know yet why the trial was continued, one could argue that the p-value the sponsor obtained, 0.013, was so close to that required at that second interim analysis, 0.014, that the Committee considered it more reasonable to continue the study to completion; indeed, we disagree with the sponsor's analyses-as previously described, they performed a parametric analysis which we concluded was inappropriate-and stopping a trial when the results are so close to the protocol required p-value, especially when the trial is so close to being completed, may even be considered reckless, for exactly these reasons (namely, for example, disputes about the appropriate analyses). We do know that the Committee discussed this in detail (and I have no doubt that these discussions among experts were sober and thoughtful) but we do not understand yet the full nature of that discussion. I am willing to accept that while there were deficiencies and that the letter of the law (particularly with respect to the absence of written informed consent for a number of patients) may have been violated, the spirit of the regulations may well have been satisfied. However, before I conclude that this was the case, the additional data I have requested should be submitted. It should be noted that, given Dr. Feeney's view, one could even argue that any trial without interim analyses is unethical, a position we have not yet adopted as an Agency.

I also cannot agree with Dr. Feeney that the duration of continued treatment is irrelevant. Reasonable people can disagree about what duration of continued

treatment with placebo may be unacceptable when definitive effectiveness results become available, but I would assert that there is a minimum duration of continued treatment (without stating what that duration would be) that most people would consider not critical. If this is granted, then the actual duration that is unacceptable becomes a matter of personal judgment.



/s/

Russell Katz
1/19/01 11:10:06 AM
MEDICAL OFFICER

MEMORANDUM

DATE: June 15, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-622/S-015

SUBJECT: Action Memo for NDA 20-622/S-015, for the inclusion of a description of MRI data in labeling for COPAXONE (glatiramer acetate)

Teva Pharmaceuticals, Inc., submitted this supplement on 8/4/99 in an attempt to extensively amend approved labeling for Copaxone. The proposed changes included descriptions of MRI data, long term effectiveness, and an amended indication.

In an Approvable letter dated 1/19/01, most of the sponsor's proposed changes were denied. The letter did acknowledge that language describing the results of Study 9003, a study in which the primary outcome was an MRI measure, could be included in the Clinical Trials sub-section of labeling. Further, the letter asked the sponsor to further address several ethical issues that were raised in relation to the conduct of this study.

Specifically, we asked the sponsor to address the following points:

- 1) This trial was conducted in several foreign countries, including 3 Canadian sites. While Copaxone was not available in Canada at the time that this trial was initiated, it became available while the trial was on-going (it was never available in the other countries). We had evidence that 2 of the 3 Canadian sites re-obtained written informed consent from their patients in the study when the drug became available, but we had no evidence that this had occurred in the third site. We asked the sponsor to obtain documentation about the re-consenting procedure at this third site.
- 2) A second, protocol specified interim analysis was performed for this trial, and the result met the protocol specified alpha level to declare the study positive. However, the study was not terminated, but instead went to completion. This entailed the continued treatment of several patients with placebo after the study had met its protocol specified endpoint. We asked the sponsor to document the process undertaken by the DSMC that resulted in the decision to continue the study.

The sponsor responded to the Approvable letter on 3/16/01. In this response, and subsequent telephone discussions with them, they have agreed to our labeling requests. Specifically, the only material changes in labeling with clinical implications will be a description of Study 9003 and the results on the primary

MRI outcome, as well as one additional graph demonstrating the time course of the change on this outcome (median cumulative number of T1 Gadolinium enhancing lesions). There have also been additional minor changes to a number of other sections of labeling.

The sponsor's response has been reviewed by Dr. Tremblay, medical officer (review dated 4/4/01) and Dr. John Feeney, Neurology Drugs Team Leader (review dated 6/1/01). Dr. Tremblay, while acknowledging residual deficiencies in the sponsor's response to the ethical concerns raised by the Division, nonetheless recommends that the application be approved. Dr. Feeney, however, recommends that the application not be approved, primarily on the basis of the fact that written informed consent was not obtained at Dr. Rice's center from patients who continued to receive double blind treatment after Copaxone became available in Canada.

The sponsor's response to the 2 questions posed in the Approvable letter related to the ethical conduct of the trial are as follows:

- 1) Eleven patients were enrolled at Dr. Rice's site in Canada, 5 before the approval of Copaxone in Canada, 5 after, and one transferred to the site (I do not know when in relation to the approval in Canada this last patient transferred to Dr. Rice's site). According to Teva, when Copaxone became available in Canada, Dr. Rice and his study coordinator verbally told **all of the patients** in his study that it had become available, but that provincial funding was not available at that time. Dr. Rice asserts that all patients were willing to continue in the trial after that point. Dr. Rice did not obtain written informed consent that incorporated this fact. Teva does not know if Dr. Rice used a "script" that described the information he gave to his patients.
- 2) The sponsor has submitted a document written by Dr. Kenneth Johnson, Chairperson of the DSMC, which describes the DSMC's rationale for the decision to continue the trial. This document is described by the sponsor as "retrospective meeting minutes", and is undated.

This memo listed several factors considered by the Committee in arriving at their decision to recommend that the trial continue:

- 1) The total number of patients left in the trial was 34, so that only about 17 would have been on placebo
- 2) The majority of these patients were within 30 days of the completion of the trial, with the longest duration left for any patient being 59 days. Based on calculations described by Dr. Johnson, the likelihood of any patient experiencing a relapse in this period of time was considered low
- 3) Dr. Johnson's memo describes the view that positive trends seen at 18-24 months in previous MS studies have disappeared with continued observation, and that continuing the conduct of the trial "...would provide important information about trends or increasing therapeutic significance that would in

turn give confidence to the treating community and the MS patient population about the value of GA therapy. The risk to the remaining patient population was considered to be small.”.

- 4) The drug was not available in the countries in which the study was being conducted.

At this point, there can be no argument about the fact that Dr. Rice did not obtain from his patients written informed consent that included the fact of Copaxone’s availability. He does assert, however, that he made all of his patients aware of this fact, that this discussion was witnessed, and that all patients affirmatively agreed to continue their participation in the trial. Apparently, none of these conversations were documented at the time that they occurred.

Although I acknowledge Dr. Feeney’s view that patients’ rights have not been protected at Dr. Rice’s center (by not having been presented with a written informed consent document describing Copaxone’s availability), I am inclined to agree with Dr. Tremblay’s current view (as expressed in his 4/4/01 memo), which is that the ethical breeches were not “pervasive” and not due to a “systematic failure” on Teva’s part. Written informed consent should have been obtained, and, failing that, a contemporaneous written record of the conversations Dr. Rice had with his patients should have been made. Since neither of these occurred, we have no documentation that patients were informed of the availability of Copaxone, and, if they were, what exactly they were told.

However, we do have Dr. Rice’s testimony that he did provide this information in conversations that were witnessed, and his warrant that patients affirmatively agreed to continue to participate in the trial. While far from being ideal, I believe this is acceptable, based on my acceptance of Dr. Rice’s testimony as being truthful (there is no evidence that there were any problems with the written informed consent procedure utilized by Dr. Rice prior to the time that Copaxone became available in Canada). I agree with Dr. Tremblay that the study was clearly not characterized by widespread disregard for ethical principles (or regulations), and I believe that the spirit of the requirement for informed consent was honored, if not the letter of the regulations.

Dr. Feeney quotes 21 CFR 314.125, which states in part that the Agency will refuse to approve an application if a trial is not conducted in compliance with the informed consent regulations “...such that the rights or safety of the human subjects were not adequately protected.”.

While the regulations make clear that written informed consent is required (there are exceptions, but they do not seem to apply here), it is my view (again, accepting Dr. Rice’s account of events), that the rights or safety of the subjects were adequately protected. It would have been desirable, of course, given that written informed consent was not obtained, for Dr. Rice to have documented the conversations with his patients, so that we could (if we wished to) examine what

he told his patients. However, we usually do not have much (or any) assurance that patients who **have** signed written informed consent forms have been adequately informed of all circumstances that would be relevant for making a truly informed decision about participation in a clinical trial (partly because we rarely examine such informed consent forms from all clinical centers participating in a trial, and partly because, regardless of what information is included in such a form, we ordinarily have no information about the [required] conversation that an investigator has with an individual patient when consent is obtained). The point is that we often rely on the investigator having engaged in an adequate informed consent procedure on no basis other than faith. While I recognize that the existence of the written informed consent form itself is supposed to provide the minimum assurance that the patient was adequately informed of the risks of participation in a trial (and that this critical piece is missing here), the conversation that is supposed to accompany the signing of the consent form is at least as important to fully informing the patient, and we ordinarily have no information about the contents of this conversation. I find it reasonable to believe that Dr. Rice adequately informed his patients (at least as adequately as we assume investigators who obtain written informed consent do) of the risks of continuing in this trial.

Regarding the reasons cited by the DSMC (more correctly by Dr. Johnson), I am convinced that the decision to continue the trial to completion was reasonable, although, again, arguable. As I noted in my 1/15/01 memo, the p-value obtained was sufficiently close to that required, and the trial so close to reaching completion, that, in my view, it was reasonable to continue the trial to obtain a definitive result. While I acknowledge that some patients received placebo longer than "necessary", had we disputed the p-value obtained (as I explained in my 1/15/01 memo), stopping the trial early would have been a major miscalculation. I am convinced that the DSMC thought about the issue in a sober manner, and came to a reasonable decision.

For these reasons, then, I will issue the attached Approval letter.

Russell Katz, M.D.

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

/s/

Russell Katz
7/11/01 08:03:18 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-622/S-015

PHARMACOLOGY REVIEW(S)

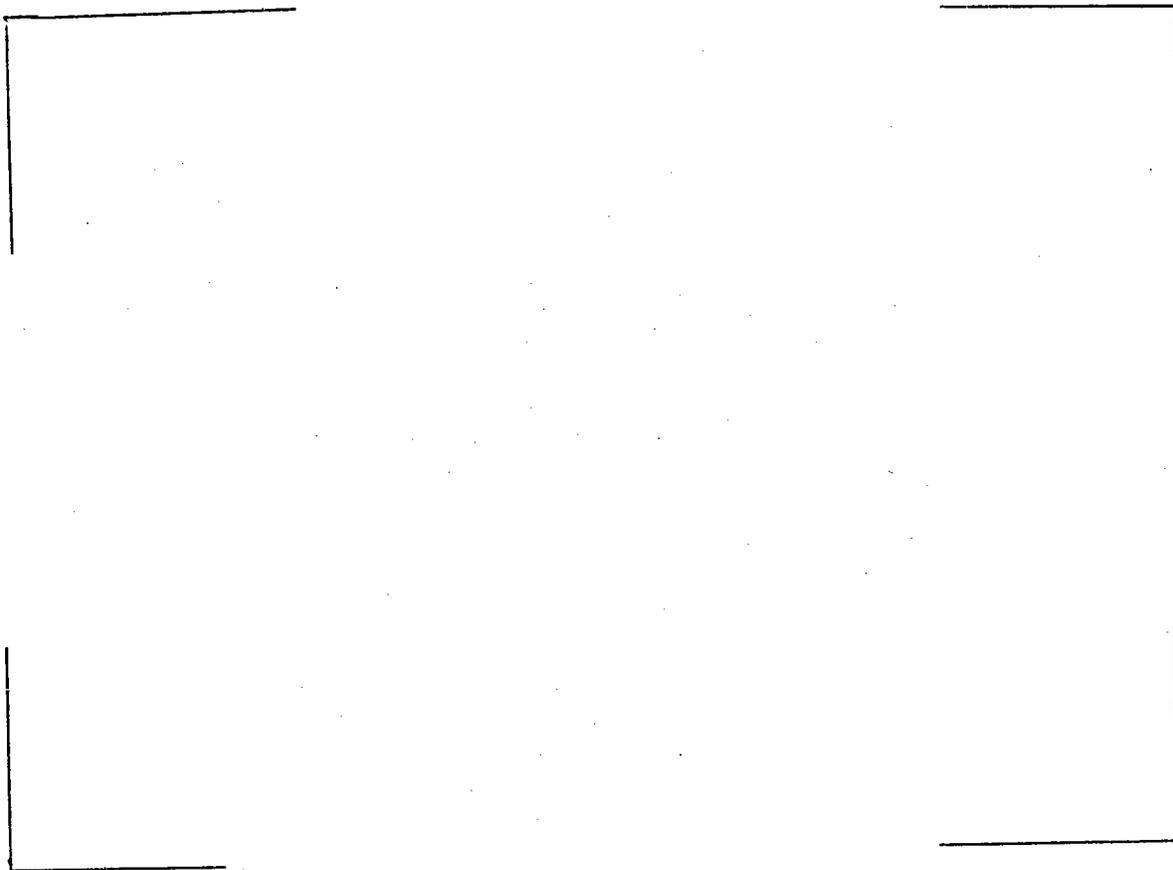
Pharmacology/Toxicology Review of Labeling Supplement

NDA:	20-622
Drug	Copaxone (glatiramer acetate for injection)
Supplement:	SLR-015
Date:	August 4, 1999
Reviewer:	Paul Roney
Review Date	November 27, 2000

Labeling Recommendations

This review examines labelling changes for Copaxone proposed in labeling supplement SLR-015 submitted on August 4, 1999. Page numbers refer to the page numbers in the unannotated draft package insert labeling. Sections that require alterations were scanned into this document. Text that should be deleted is indicated by ~~striketrough~~; text that should be added is indicated by underline. Reviewer comments in **bold** follow proposed changes.

[]



1 page(s) of draft labeling has been removed from this portion of the review.

Pharmacology Review



Paul Roney

cc: NDA 20-622
Fitzgerald
Roney
Wheelous
HFD-120

/s/

Paul Roney
11/27/00 04:08:08 PM
PHARMACOLOGIST

Glenna Fitzgerald
12/21/00 01:57:29 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-622/S-015

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#: 20-622
DRUG COMPANY: TEVA Pharmaceuticals USA
NAME OF DRUG: Copaxone Injection
INDICATION: Multiple Sclerosis
STUDIES REVIEWED: Studies [] and 9003
DOCUMENTS REVIEWED: Sponsor's NDA Labeling Supplement
MEDICAL REVIEWER Gerald Tremblay, M.D.

1. Introduction

Copaxone was approved in 1996 based on two randomized, double-blind, placebo-controlled studies. A new MRI study, 9003, was conducted after Copaxone was approved. This study intended to determine whether the benefit of Copaxone that was seen in clinical parameter in the first two studies was also reflected in the MRI parameters.

In this submission, the sponsor requested labeling amendments to include the efficacy results from Study 9003. []

[]

The primary purpose of this review is to evaluate the design and the efficacy results of Study 9003. The secondary purpose of this review is to discuss the proposed changes in the labeling for studies 9003 []

2. Specifications and Findings of Study 9003

2.1 Objectives

The objectives of this trial are to determine over the first 36 weeks of a placebo-controlled phase the effect of glatiramer acetate on MRI measured disease activity.

2.2 Study Design

This was a multi-national, multi-center, randomized, double-blind, placebo-controlled trial of 36 weeks duration. The study drug was subcutaneously administered at a single daily dose of either 20 mg Copaxone or 40 mg mannitol as placebo. About 200 relapsing-remitting MS patients were planned to be included and randomized in equal numbers to receive either daily subcutaneous injection of 20 mg Copaxone or placebo. A total of 485 patients were screened for up to 28 days prior to the initiation of the treatment. Of these patients, 239 patients were recruited at 29 centers and entered the trial. The total duration of the study was 9 months. During this period 10 visits were performed: a baseline visit

and 9 monthly visits until the completion of the study. After 36 weeks all patients were to continue with only the active drug treatment, as an open label trial, for an additional 36 weeks for a total of 72 weeks.

Serial monthly MRI scans were to be performed at screening (month -1) baseline (month 0) and during the 9 months of double-blind phase. Neurological examinations were to be performed at screening, baseline, and then every 12 weeks.

The first patient was enrolled on 12th March, 1997, and the last observation was taken on 19th August, 1998.

2.3 Study Management

At each center there were two neurologists: the treating neurologist was responsible for routine evaluations and the examining neurologist was blinded to all the patients' records and was responsible for the clinical neurological evaluation. These two investigators worked independently. In addition, the study site personnel also included two radiologists, an MRI technician and a clinical coordinator who were blinded to the patients' assignments.

The MRI reading was performed centrally and independently of the centers. All personnel were unaware of the patients' assignments, as stated by the sponsor.

2.4 Main Inclusion Criteria

Patients must meet all inclusion criteria in order to be eligible for the study:

- The patient must have clinically definite MS as defined by Poser et al.
- The patient must be of the relapsing-remitting type.
- The patient must be relapsing-free and off steroids at least 30 days prior to the pre-enrollment MRI scan at screening.
- The patient must have been diagnosed with relapsing-remitting MS and the documented onset of first attack within 12 months prior to study entry is available.
- The patient must be age of 18-50 years inclusive.
- The patient must be ambulatory, with EDSS score of 0-5 inclusive.
- The patient must have at least one documented relapse in the two years prior to study entry.
- The patient must have at least one Gd-enhanced lesion in the pre-enrollment MRI scan, at screening.

2.5 Efficacy Evaluation

All trial end-points were to be derived from the MRI measurements. No clinical efficacy parameters were planned or assessed during the 9-month double-blind period. The intent-to-treat patient population was the primary data set to be used in all efficacy analyses and missing values were to be imputed by method of LOCF. Results from other patient

cohorts and imputation methods that were used by the sponsor are not reported in this review.

2.5.1 Primary Efficacy Parameter and Primary Analysis

The primary outcome was the total number of Gd-enhanced lesions in T1-weighted images in the first 36 weeks. The total number of Gd-enhanced lesions represents the sum of these lesions counted in all scans performed during the 9 month double-blind period.

Based on the protocol, an analysis of baseline adjusted covariance (ANCOVA, SAS proc GLM) was to be used to compare the two treatment groups for this primary end-point incorporating terms for treatment and center. The treatment-by-center interaction term was not to be included in the model if it was not statistically significant (i.e., if $p > 0.05$). Covariates to be used in the analysis were baseline pre-randomization number of Gd-enhancing T1-weighted lesions, baseline EDSS score, number of relapses in the 2-years prior to trial entry and disease duration. Demographic data including age and sex were also to be used as covariates in the analysis.

It was stated in the Final Data Analysis Plan that in order to validate the results and conclusions of the above analysis, the log transformation for the total number of T1 Gd-enhanced lesions (+1) and the rank transformation were to be performed. A Quasi-Likelihood Poisson model was also planned.

2.5.2 Secondary Efficacy Variables

The secondary outcome measures include:

- a. The proportion of patients with Gd-enhanced lesions in T1-weighted images
- b. The total volume of Gd-enhanced lesions in T1-weighted images
- c. The number of new Gd-enhanced lesions in T1-weighted images
- d. The total volume of lesions in T2-weighted images
- e. The total number of new lesions detected in T2-weighted images
- f. The total volume of hypointense lesions in unenhanced T1-weighted images

2.5.3 Correlation between MRI and Neurological Indices

In addition to the above primary and secondary efficacy variables, it was stated in the Final Data Analysis Plan that the correlation between MRI and neurological indices including relapse rate, proportion of relapse-free patients, time to first relapse, and change from baseline in EDSS scores and in Ambulation Index was to be explored in summary statistics. No statistical testing was proposed for any clinical parameters.

2.6 Interim Analysis

Two interim analyses were planned and were to be performed after at least 65 and 130 of the patients have completed 9 month of double-blind treatment. For the first interim analysis, treatment effect was to be considered statistically significant if the p-value is

0.00052334 or less. For the second interim analysis a p-value of 0.014182 or less was required. The final analysis would require a p-value of 0.045226. These p-values represent the use of O'Brien-Fleming's correction to type I error.

The two interim analyses were performed when the first 80 patients and the first 160 patients completed double-blind phase. The sponsor reported that only the primary endpoint was analyzed on both occasions, using the ITT cohort and LOCF approach. The first and the second interim analysis results were presented to the sponsor's advisory committee on March 17, 1998 and June 14, 1998, respectively. The p-values obtained were 0.0158 and 0.0131, for the first and the second interim analysis, respectively, using the primary ANCOVA model. Although the p-value for the second interim analysis reached predefined significance level, the sponsor decided not to stop the trial. The company's responsible biostatistician and the members of the External Advisory Committee were unblinded to both interim analysis results.

2.7 Results: Sponsor's Analysis

2.7.1 Patient Disposition

A total of 485 patients was screened, and among them 239 patients (49%) entered study and were randomized to Copaxone 20 mg (119 patients) or placebo (120 patients). A total of 14 patients (7 in each group) discontinued the trial prematurely (Table 5).

Table 5. Termination Reasons (from sponsor)

Treatment	Copaxone N (%)	Placebo N (%)
All Patients	119 (100)	120 (100)
9 Month Completion	112 (94.1)	113 (94.2)
Adverse Experience	3 (2.5)	2 (1.7)
Patient Refusal to Continue	0 (0)	2 (1.7)
Consent Withdrawn	4 (3.4)	0 (0)
Lost of Follow-Up	0 (0)	1 (0.8)
Other	0 (0)	2 (1.7)

2.7.2 Patient Baseline and Demographic Characteristic

Summary statistics of demographic characteristics and baseline disease characteristics are presented in Table 7. The sponsor reported that no significant differences were found between the groups with respect to the baseline demographic characteristics. All clinical parameters assessed at baseline were comparable between the two groups.

Table 7. Demographic Characteristics and Baseline Disease Characteristics (from sponsor)

	Capaxone N=119	Placebo N=120
Age		
Mean (SD)	34.1 (7.4)	34.0 (7.5)
Range	19 – 50	18 – 48
Sex		
Male	27	33
Female	92	87
Weight (kg)		
Mean (SD)	66.2 (12.7)	67.0 (14.3)
Range	44 – 105	45 – 124
Age at 1st symptom		
Mean (SD)	27.2 (6.8)	26.7 (7.2)
Median	25.0	26.0
Baseline AI		
Mean (SD)	1.1 (0.9)	1.2 (1.0)
Median	1.0	1.1
Baseline EDSS		
Mean (SD)	2.3 (1.1)	2.4 (1.2)
Median	2.0	2.0
Baseline Sum FS		
Mean (SD)	4.1 (2.7)	4.7 (3.3)
Median	4.0	4.0
Prior 2-yr Relapses		
Mean (SD)	2.8 (1.8)	2.5 (1.4)
Median	2.0	2.0
Time from Diagnosis of MS (month)		
Mean (SD)	57.4 (46.7)	59.3 (45.6)
Median	44.0	45.0
Time from 1st Symptom (month)		
Mean (SD)	95.1 (65.5)	99.5 (65.5)
Median	79.0	80.5

The assessments with regard to baseline MRI characteristics are displayed in Table 4. The sponsor reported that the patient distribution to treatment groups by MRI characteristics was balanced, and the comparability was verified by the t-test and Kruskal-Wallis test. As noted by the sponsor, there was a slight difference between the two groups in the baseline T1 Gd-enhanced lesion volume, but the difference was not statistically significant.

Table 4. Patients' Baseline MRI Characteristics (from sponsor)

Baseline MRI Parameter	Capaxone (n=119)	Placebo (n=120)
New T1 Lesions		
Mean (SD)	2.5 (3.5)	2.6 (4.1)
Median	1.0	1.0
New T2 lesions		
Mean (SD)	1.0 (1.5)	1.2 (1.7)
Median	1.0	1.0
# of T1 Lesions		
Mean (SD)	4.2 (4.8)	4.4 (7.1)
Median	3.0	2.0
T1 Lesion Volume		
Mean (SD)	569.4 (705.8)	732.9 (2201.4)
Median	329.0	230.0
T1 Hypointense Lesion Volume		
Mean (SD)	3371.5 (3850.8)	3958.2 (4944.4)
Median	1817.0	2879.5
T2 Lesion Volume		
Mean (SD)	20004.3 (17239.0)	20535.9 (18760.5)
Median	14133.0	16318.5

The sponsor reported that most patients had at least one active lesion at baseline. Only about 20% were T1 lesion free at baseline although they exhibited new active lesions at baseline as screening. Most patients also exhibited new active lesions at baseline as compared with screening, however, not all of these active lesions were already seen as new T2 lesions. The proportion of patients with/without lesions at baseline is presented in Table 5.

Table 5. Number (percentage) of Patients without MRI Lesion (from sponsor)

Baseline MRI Parameter	Capaxone N/Total (%)	Placebo N/Total (%)	All N/Total (%)
T1 Lesion-free	21/119 (17.6)	22/120 (18.3)	43/239 (18.0)
T1 New Lesion-free	42/115 (36.5)	43/118 (36.4)	85/233 (36.5)
T2 New Lesion-free	56/115 (48.7)	58/118 (49.2)	114/233 (48.9)

2.7.3 Concurrent Medications

The sponsor reported that about 80% in both groups administered additional medications during the trial period. The most commonly used medications were various types of corticosteroids (which were taken during relapses in most cases). No major differences were found between treatment groups in the overall incidences of medication consumption. The two treatment groups were compared for their systemic steroid intake. The proportions of patients in the Copaxone and placebo groups who consumed systemic steroids during the study were 37.0% and 39.2%, respectively.

2.7.4 Efficacy Results

2.7.4.1 Primary Efficacy Analysis

The primary endpoint, the total number of Gd-enhanced lesions represents the sum of these lesions counted in all serial monthly scans (excluding baseline) performed during the nine months of the double-blind period for each patient. A baseline-adjusted analysis of covariance (ANCOVA) was used to compare the two groups for this primary endpoint, incorporating terms for treatment and center as main effects. Covariates that were used in the analysis were the baseline pre-randomization number of T1 Gd-enhanced lesions, baseline EDSS score, number of relapses in the two-year prior to trial entry and disease duration. Demographic data including age and sex were also used as covariates.

The sponsor reported that the interaction between the treatment and center was found not significant. In order to validate the results, the following were employed:

- Log transformation for the total number of Gd-enhanced lesions (+1)
- Rank transformation for the total number of Gd-enhanced lesions
- Poisson regression

The results were analyzed according to ITT cohort in two ways: the LOCF imputation and observed cases. Seventeen statistical models were employed to test the significance level of the primary endpoint results. The distributions of values for the primary endpoint for patients in both groups were skewed. Therefore, although the formal predefined analysis refers to comparison of adjusted means, to further confirm the results, data were also analyzed and presented using median values. Regardless of the statistical models used, results always reached statistical significance, as reported by the sponsor.

The total number of the T1 Gd-enhanced lesions was reduced by 29% (adjusted mean) following nine months of Copaxone treatment as compared with the placebo group (LOCF). The mean difference over placebo was -10.84 (95% CI: -17.97, -3.71). This difference was statistically significant ($p=0.0032$). The median total number of T1 Gd-enhanced lesions was 11 for the Copaxone group and 17 for the placebo group.

2.7.4.2 Analysis of Secondary Efficacy Variables

The sponsor reported that the results of all secondary endpoints, excluding the proportion of T1 Gd-enhanced lesion free patients and total number of the hypointense lesions revealed a statistically significant difference between the Copaxone group and the placebo group. The results are presented for the ITT cohort using LOCF analysis.

Table 23. Secondary Efficacy Endpoints (from sponsor)

Parameter	p-value
Proportion of T1 Gd-enhancing lesion-free patients	0.0948
Total number of new Gd-enhancing lesions	0.0029
Monthly median change from baseline in T1 lesion volume	RMA(rank) 0.0098
Total number of new T2 lesions	0.0029
Change from baseline in T2 lesion volume	RMA(rank) 0.0245
Change from baseline in hypointense lesion volume	RMA 0.8974

The Proportion of T1 Lesion-Free patients: The sponsor reported that the proportion of patients who were T1 lesion free during the entire study was not statistically significantly different between the two treatment groups.

Total Number of New T1 Gd-Enhancing Lesions: The sponsor found that the total number of new T1 lesions during the trial was significantly smaller in the Copaxone group compared to placebo group (p=0.0029). The medians of the total number of new T1 lesions were 9.0 and 13.5 for the Copaxone group and placebo group, respectively.

Total Number of New T2 Lesions: The sponsor reported that the total number of new T2 lesions was statistically significantly different between the two treatment groups (p=0.0029) following nine months of treatment of Copaxone. The medians of the total number of new T2 lesions were 5.0 and 8.0 for the Copaxone group and placebo group, respectively.

Monthly Median Change from Baseline in T1 Gd-Enhancing Lesion Volume: The sponsor reported that monthly median change from baseline to termination in the volume of T1 Gd-enhancing lesions was significantly different for the two treatment groups. The corresponding p-value from the repeated measurement analysis was reported as 0.0098.

Monthly Median Change from Baseline in T2 lesion Volume: It was reported that monthly median change from baseline to termination in T2 lesion volume was significantly different for the two treatment groups. The corresponding p-value from the repeated measurement analysis was reported as 0.0245.

T1 Hypointense Lesion Volume: No statistically significant difference was found in the T1 hypointense lesion volume between the treatment groups.

2.7.4.3 Clinical Effects

The possible relationship between MRI parameters and clinical MS related indices collected during the double-blind phase was to be explored in the form of summary statistics. However, the sponsor reported that following nine months of treatment, it was found that a significant effect on the number of relapses has been seen. A baseline-adjusted analysis of covariance (ANCOVA) was used to compare the two groups. The

adjusted mean relapse rate in the Copaxone group was 33% lower than that was found in the patients on placebo (0.51 vs. 0.76). This result was statistically significant (p=0.0117).

2.8 Reviewer's Analysis

2.8.1 Primary Efficacy Analysis

The primary analysis performed by the sponsor was verified, and the same p-value of 0.0032 was obtained by this reviewer. This p-value of 0.0032 was not considered as a valid evidence in establishing the efficacy because the normal assumption was violated in the parametric model from which the p-value was obtained. A p-value of 0.0184 from the rank-transformed data and a p-value of 0.0391 from the log-transformed data were also reported by the sponsor. However, these results from the sponsor's analyses are difficult to be interpreted because the total numbers of T1 lesions at baseline and during the double-blind phase are on two different scales. This reviewer applied protocol specified primary analysis with the following differences from the sponsor:

1. One patient (patient number 3417) did not have any post-baseline measurements. This patient was included in the sponsor's analysis (baseline measure was carried forward for all 9 monthly measure during double blind phase) and was excluded from the reviewer's analysis.
2. When applying the log transformation, only the endpoint of total number of T1 lesions was transformed to log scale in the sponsor's analysis. Therefore, the number of T1 lesions at baseline and during the trial were on two different scales. In the reviewer's analysis, both baseline T1 lesions and T1 lesions during the trial were transformed to log scale.
3. When applying the rank transformation, only the endpoint of total number of T1 lesions was transformed to ranks in the sponsor's analysis, leaving the baseline T1 lesion number as original. In the reviewer's analysis, the rank transformation was applied to the total of the monthly differences of the number of T1 lesions at each month during the trial and the number of T1 lesions at baseline. The covariate of baseline T1 lesion number was omitted in the model.

Results from Reviewer's Analysis

The primary analysis of ANCOVA model was first applied to the total number of T1 lesions. One patient with no post-baseline T1 measures was excluded from the analysis. The p-value of the treatment effect was 0.0026. However, it was indicated by the Shapiro-Wilk test that the assumption of normality was not satisfied (p<=0.0001). Based on the protocol and Data Analysis Plan, the log and rank transformations were employed.

As noted above, this reviewer applied log transformation to the endpoint as well as the baseline values (log (baseline+1)). The rank transformation was applied to the total of monthly differences from the baseline. In both cases, the interaction of treatment and center was not significant, and was therefore removed from the model.

After the log transformation the residual of the model was tested again for normal assumption. A p-value of 0.5282 was obtained, indicating that the normal assumption was no longer violated. The treatment effect carries a p-value of 0.0044 in favor of Copaxone group. The baseline T1 lesion number has a significant effect on the number of T1 lesions during the trial ($p < 0.0001$). In the analysis of rank-transformed data, a p-value of 0.0030 was obtained for the treatment effect of Copaxone.

The value of the primary efficacy endpoint was broken down to subgroups by demographic characteristics and baseline T1 lesion presence in order to evaluate whether or not the efficacy results were balanced by those subgroups.

It appears that the numerical difference between the Copaxone group and placebo group in the total number of T1 lesions are consistent across the subgroups that are studied. The following table presents the summary statistics of the total number of T1 lesions during the 9-month trial by indicated subpopulations.

Table 1. Summary Statistics of the Total Number of T1 Lesions by Subpopulations (9 Month Double Blind Phase)

		Copaxone (n=118)	Placebo (n=120)
Total # of T1 lesions			
All patients	Mean (SD)	24.08 (34.19)	36.29 (54.48)
	Median	11	17
Male	n	27	33
	Mean (SD)	22.15 (26.87)	40.24 (44.89)
Female	Median	8	21
	n	91	87
Age ≤ 34 ^I	Mean (SD)	24.65 (36.19)	34.79 (56.56)
	Median	12	17
Age > 34	n	61	61
	Mean (SD)	23.80 (27.76)	37.62 (47.99)
Baseline T1 free	Median	10	20
	n	57	59
Baseline T1 present	Mean (SD)	24.37 (40.21)	34.92 (59.00)
	Median	12	17
Total monthly differences from baseline	n	21	22
	Mean (SD)	7.81 (10.99)	11.68 (14.04)
Baseline T1 present	Median	5	7.5
	n	97	98
Total monthly differences from baseline	Mean (SD)	27.60 (36.46)	41.82 (57.42)
	Median	14	21
Total monthly differences from baseline	Mean (SD)	-13.53 (31.77)	-3.23 (37.09)
	Median	-7	-1

I. 34 was the median age for all patients.

Based on the results of the above analyses, this reviewer would conclude that the significance of the treatment of Copaxone on the total number of T1 lesions has been reached for this 9-month study.

2.8.2 Analysis of Secondary Efficacy Measures

All secondary measures of efficacy were analyzed using the methods specified in the Data Analysis Plan (DAP). A summary table of results is presented at the end of this section.

The proportion of patients with Gd-enhanced lesions in T1-weighted images

The proportion of patients with Gd-enhanced lesions in T1-weighted images was to be analyzed using baseline adjusted repeated measures analysis (SAS Proc catmod). The covariates that were to be included in the model were not clearly stated, and therefore, the analysis was not performed by this reviewer. As reported by the sponsor, the p-value of the drug effect was 0.0948, which did not reach the statistical significance.

The number of new lesions in T1-weighted and T2-weighted images

The number of new Gd-enhanced T1 lesions and the number of new T2 lesions were to be analyzed in a similar way to the primary efficacy variable of total number of T1 lesions, as specified in DAP. The parametric model of ANCOVA was used first, and for both analyses of new T1 lesions and new T2 lesions the normal assumption was not met based on the Shapiro-Wilk test on the residuals ($p \leq 0.0001$ for both T1 and T2). After the log-transformation, the normal assumption was no longer violated in both analyses of T1 and T2 lesions ($p = 0.4905$ for T1 and $p = 0.2349$ for T2).

For the number of new T1 lesions, the drug effect had a p-value of 0.0048 from the log-transformed data analysis. The analysis on the rank transformed data showed a p-value of 0.0154 for the drug effect.

As for the number of new T2 lesions, the drug effect had a p-value of 0.0073 from the log-transformed data analysis and a p-value of 0.0769 from the rank-transformed data analysis.

The total volumes of T1 and T2 lesions

As specified in the DAP, the total volume of T1 Gd-enhanced lesions and the total volume of T2 lesions were to be analyzed similarly as changes from baseline at each visit using repeated measures analysis of covariance (SAS Proc GLM). The model would include effects of treatment, center, and baseline value of the volume.

For both analyses of T1 lesion volumes and T2 lesion volumes, the normal assumption for the parametric model stated above was violated based on the Shapiro-Wilk's test on the residuals of the model ($p \leq 0.0001$ in both analyses). The log transformation was not

applied because of negative values of the difference from baseline. Therefore, only rank transformation was applied in both analyses of T1 lesion volume and T2 lesion volume.

After the rank transformation, the p-value of the drug effect was found to be 0.0105 in the analysis of T1 volume, and a p-value of 0.0259 was obtained in the analysis of T2 lesion volume.

The total volume of hypointense lesions in unenhanced T1-weighted images

The total volume of T1 hypointense lesions was to be analyzed in a similar way to volumes of T1 and T2 lesions, which was a repeated measure analysis of covariance on the monthly differences from the baseline. A p-value of 0.9386 was obtained from the parametric model and a p-value of 0.8916 was obtained from the rank-transformed data analysis.

Table 3. Summary of Efficacy Analysis from Secondary Measures

Secondary Measure	Parametric Model (p-value from normal test)	Log-transformed	Rank-transformed
Proportion	N.S. ¹	N.A. ²	N.A. ²
T1 lesion volume	0.0340 (0.0001)	Not analyzed	0.0105
T2 lesion volume	0.7592 (0.0001)	Not analyzed	0.0259
# of new T1 lesions	0.0016 (0.0001)	0.0048	0.0154
# of new T2 lesions	0.0197 (0.0001)	0.0073	0.0769
T1 Hypo volume	0.9386 (0.0001)	N.A.	0.8916

1. N.S.: not significant

2. N.A.: not applicable

Multiplicity Adjustment for Secondary Efficacy Measures

There are six secondary efficacy variables altogether. No adjustment method was given as how to win the secondary efficacy variables. This reviewer would then apply the commonly used Bonferroni adjustment (dividing 0.05 by 6) to the six secondary parameters. The resulting significance level is 0.0083 for any of the six secondary efficacy variables.

Two of the secondary efficacy variables, the total number of new T1 lesions and the total number of new T2 lesions, reached the adjusted significance level in the analysis using the log-transformed data. These two variables did not reach the adjusted significance level in the analysis of rank transformed data. Other secondary efficacy variables did not reach this significance level.

Differences in Analyses and Results Presented in the Final Report and Proposed Labeling

There were substantial differences in the efficacy results obtained by this reviewer and those presented in the final report and the proposed labeling. The source of the differences was primarily contributed by using different analysis methods other than the

analysis specified in the protocol by the sponsor. For example, in the final report where the sponsor reported the results for new T1 lesions (page 68 Figure 13), it was reported that the drug effect carried a p-value of 0.0029 using RMA and drug*time carried a p-value of 0.0732. However, the protocol specified analysis for this variable is the ANCOVA on the total of the 9 monthly observations of the new T1 lesions instead of repeated measurement analysis on the 3 trimester measures of the new T1 lesions.

2.9 Summary of Efficacy Results

In summary, this MRI study has provided sufficient evidence that Copaxone-treated patients had fewer T1 Gd-enhancing lesions than the placebo-treated patients during the trial. It appears that Copaxone-treated patients might also have had the benefits of having fewer new T1 Gd-enhancing lesions and new T2 lesions as compared to placebo-treated patients, although a definitive conclusion can not be reached. The study did not provide sufficient evidence that Copaxone is efficacious regarding to the variables of proportion of patients that were lesions-free, T1 lesion volume, and T2 lesion volume. There is no evidence that Copaxone has any effect on T1 hypointense lesion volume.

The effect of corticosteroids on the efficacy variables was not evaluated in the reviewer's analysis because the data of patient's corticosteroid use was not available to the reviewer.

3.0 Comments Regarding the MRI Study 9003 Proposed Labeling

Study 9003 was completed after the Copaxone was approved. In this NDA labeling supplement the sponsor proposed to include the results of this MRI study 9003 into the original approved labeling. Here in this review, only the section **CLINICAL PHARMACOLOGY/Clinical Trials** in the proposed labeling that related to the efficacy results is discussed.



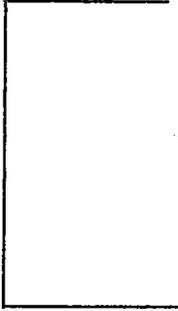
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Statistical Review



Sharon Yan, Ph.D.
Mathematical Statistician

Concur:

Kun Jin, Ph.D.
Team Leader

George Chi, Ph.D.
Director, Division of Biometrics I

Cc: NDA# 20-622
HFD-120/Dr. Katz
HFD-120/Dr. Feeney
HFD-120/Dr. Tremblay
HFD-120/Ms. Wheelous (CSO)
HFD-120/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Yan

This review consists of 16 pages. 12/21/00

**Appears This Way
On Original**

/s/

Sharon Yan
1/12/01 02:12:46 PM
UNKNOWN

Kun Jin
1/12/01 03:24:30 PM
UNKNOWN

George Chi
1/12/01 03:38:41 PM
BIOMETRICS

Sharon, I think you have done an excellent review. It is very thorough, and used the data to prove your points. The review is written fairly succinctly. Keep up the good work

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-622/S-015

**CLINICAL PHARMACOLOGY/
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 8/4/99, 10/16/00

NDA: 20-622/SLR-015
Name of Drug: Copaxone Injection, 20 mg/ml Glatiramer Acetate
Sponsor: TEVA Pharmaceuticals, USA
Indication of Drug: Multiple Sclerosis
Type of Submission: Labeling Change Supplement
Reviewer: Hong Zhao, Ph.D.

Introduction

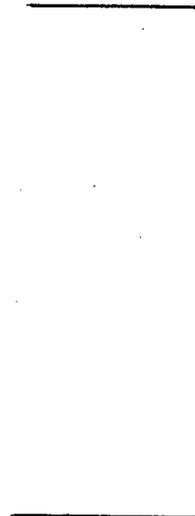
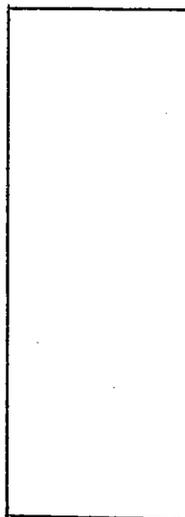
Glatiramer acetate for subcutaneous injection (Copaxone[®]) is approved for treatment of relapsing-remitting multiple sclerosis (NDA 20-622). This supplement is for labeling changes to the following sections: CLINICAL PHARMACOLOGY (Mechanism of Action, Pharmacokinetics, and Clinical Trials), INDICATIONS AND USAGE, PRECAUTIONS (Considerations Regarding the Use of a Product Capable of Modifying Immune Responses, Drug Interactions, and Carcinogenesis, Mutagenesis, Impairment of Fertility), and ADVERSE REACTIONS (Chest Pain).

Clinical Pharmacology and Biopharmaceutics Related Labeling Changes

Changes under CLINICAL PHARMACOLOGY (Pharmacokinetics subsection) have been reviewed (OCPB review dated May 2, 2000). □

□

□



— page(s) of draft
labeling has been
removed from this
portion of the review.

Clinical Pharmacology and Biopharmaceutics

Please convey this Comment to the Medical Officer.

Hong Zhao, Ph.D. _____

RD/FT Initialed by Raman Baweja, Ph.D. _____

cc: NDA 20-622 (Copaxone Injection, Labeling Change), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

/s/

Hong Zhao
12/13/00 10:18:40 AM
BIOPHARMACEUTICS

Raman Baweja
12/13/00 11:27:40 AM
BIOPHARMACEUTICS

38.1

COMPLETED MAY 02 2000
MAY 2 2000
JW
5/3/00

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Submission Dates: 8/4/99
OCPB Receipt Date: 4/13/2000

NDA: 20-622/SLR-015
Name of Drug: Copaxone Injection, 20 mg/ml Glatiramer Acetate
Sponsor: TEVA Pharmaceuticals, USA
Indication of Drug: Multiple Sclerosis
Type of Submission: Labeling Change Supplement
Reviewer: Hong Zhao, Ph.D.

Introduction

Glatiramer acetate for subcutaneous injection (Copaxone®) is approved for treatment of relapsing-remitting multiple sclerosis (NDA 20-622). This supplement is for labeling changes to the following sections: CLINICAL PHARMACOLOGY (Mechanism of Action, Pharmacokinetics, and Clinical Trials), INDICATIONS AND USAGE, PRECAUTIONS (Considerations Regarding the Use of a Product Capable of Modifying Immune Responses, Drug Interactions, and Carcinogenesis, Mutagenesis, Impairment of Fertility), and ADVERSE REACTIONS (Chest Pain).

Clinical Pharmacology and Biopharmaceutics Related Labeling Changes

Under CLINICAL PHARMACOLOGY (Pharmacokinetics Subsection) the following paragraph is deleted:

Pharmacokinetics studies in humans have not been performed. It is assumed, however, based in part on the results of animal studies, that a substantial fraction of subcutaneous injection of glatiramer acetate is hydrolyzed locally. Some fraction of injected material is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

And the following paragraph is added:

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support the assumption that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Nevertheless, large fragments of glatiramer acetate can be active and are still recognized by glatiramer acetate reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some

Literature Review

In supporting the above proposed change, the sponsor provided three references (see Appendix I-III).

Reference 1 is an abstract with study objective to better define the mechanism of action of Copolymer-1 (Glatiramer acetate, Cop-1) as an immunomodulatory treatment for multiple sclerosis (MS). According to the author, the study results showed that Cop-1 inhibited the proliferation of myelin basic protein (MBP)-specific, but not foreign antigen-specific human T cell clones (TCC). MBP-induced T cell receptor (TCR) down modulation was inhibited by Cop-1 in a dose-dependent manner.

Reference 2 is a study report. Three beagle dogs received s.c. injection of Copaxone at a dose of 3 mg/kg. The major pharmacokinetic parameters are shown in the following table:

	T _{max} (h)	C _{max} (ng/ml)	AUC ₀₋₂₄ (ng.h/ml)
Dog #1	0.5	340	1124
Dog #2	0.75	243	2220
Dog #3	1.0	157	980
Mean±SD	0.75±0.25	247±92	1441±678

Glatiramer acetate could be detected in the three dogs within 5-10 minutes of injection. In two dogs, the serum levels were back to baseline within 6 hours.

Reference 3 is a study report. The sponsor conducted this pilot study to quantify glatiramer acetate in human blood after subcutaneous (S.C.) administration of a 60 mg dose, i.e. three times the therapeutic dose, to healthy male volunteers. Glatiramer acetate concentration in serum was determined by a Competition Enzyme-Linked Immunosorbent Assay (ELISA) with LOQ of 50 ng/ml. Glatiramer acetate could be quantitatively detected in nine out of the 17 subjects who received Copaxone. In all of these subjects, the T_{max} was between 15 and 30 minutes; C_{max} was in the range of 69 to 605 ng/ml and AUC was ranging from 1,644 to 67,532 ng.min/ml. In all the subjects with measurable blood glatiramer acetate concentrations, the levels returned to baseline within 30-60 minutes post infusion. However, in four subjects quantifiable amounts of glatiramer acetate appeared again in the serum at a later time point of 240 or 360 minutes.

The results of this study indicate that in humans, small fraction of glatiramer acetate is absorbed from the site of injection and rapidly removed from the circulation.

Comment

The above references support the change in the PK labeling of Copaxone under the Clinical Pharmacology Section of Copaxone labeling. Therefore, this change proposed by the sponsor is acceptable.

Please convey this Comment to the Medical Officer.

Hong Zhao, Ph.D. Hong Zhao 5/1/2000

RD/FT Initialed by Raman Baweja, Ph.D. R. Baweja 5/2/2000

cc: NDA 20-622 (Copaxone Injection, Labeling Change), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

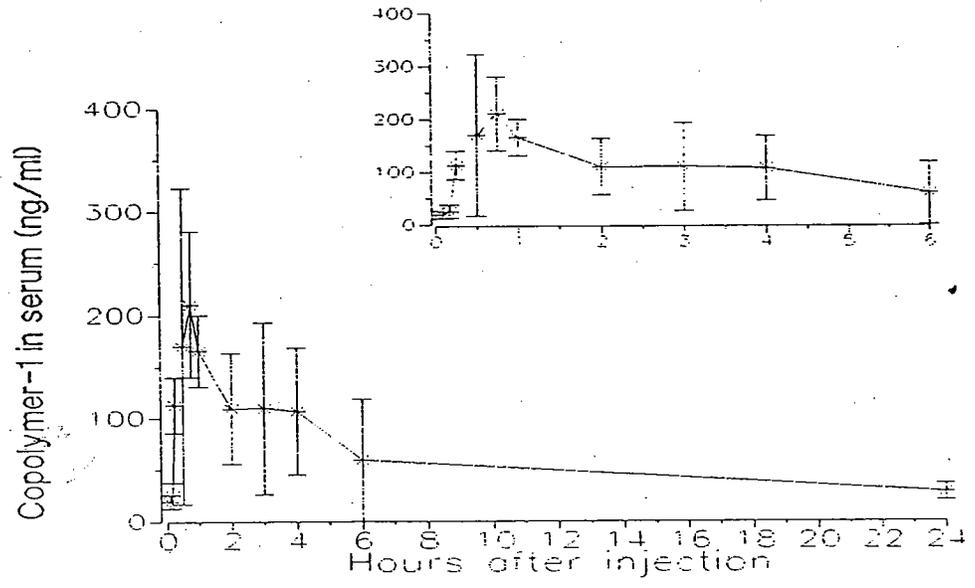
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Clinical Pharmacology / Biopharmaceutics

to comply with copyright
laws.

Gran, B., Tranquill, L., et al. Copolymer-1 Modulates Autoreactive, Myelin Basic Protein-Specific Human T Cells and Induces Specific T-Helper 2 T Cell Clones. *Neurology* 1999; **52 (Suppl 2)**: A264.

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Fig. 4. Pharmacokinetic profile of copolymer-1 in beagle dogs. Mean \pm S.D levels of copolymer-1 in the serum of 3 beagle dogs following S.C injection at a dose of 3 mg/kg. The insert expands the range of 0-6 hours.

Table 4: Mean level of copolymer-1 in the 3 dogs sera (ng/ml).

Time	Dog 1	Dog 2	Dog 3	Average	S.D
	Mean				
5 min	14.7	16.1	27.4	19.40	6.96
10 min	39.2	14.5	23.3	25.67	12.52
15 min	117.9	83.7	137.4	113.00	27.18
20 min	61.9	79.3	123.0	88.07	31.48
30 min	340.2	44.8	125.0	170.00	152.75
45 min	258.2	243.4	129.7	210.43	70.31
1 hr	204.4	137.0	155.8	165.73	34.78
2 hr	94.1	169.3	65.6	109.67	53.57
3 hr	77.5	204.3	47.4	109.73	83.27
4 hr	37.1	152.4	131.7	107.07	61.47
6 hr	35.3	126.7	16.3	59.43	59.02
24 hr	28.8	19.8	35.5	28.03	7.88

The calculated pharmacokinetic parameters for each dog and the calculated means are listed in table 5.

Copolymer-1 could be detected in the three dogs within 5-10 minutes of injection. The mean maximal serum level (C_{max}) was 246.5 ng/ml and the individual C_{max} values were 340.2, 243.4 and 156.8 ng/ml for dogs 1, 2 & 3, respectively. T_{max} was 30, 45 and 60 minutes. A second peak, (a shoulder of a peak in dog #1) could be detected at 3 hours. The nature of this peak is unknown.

The serum concentration of the drug after 24 hours was under the Limit of Quantification (LOQ) of the method as determined in human/rat serum (25-50 ng/ml). In two dogs, # 1 & 3, the serum levels were back to baseline within 6 hours.

The AUC₀₋₂₄ was calculated using the trapezoidal rule. The mean value was 1441 ± 678 ng·h/ml and the individual values were: 1124, 2220 and 980 ng·h/ml for dogs # 1, 2 and 3, respectively.

Table 5. Pharmacokinetic parameters in the 3 dogs

	dog#1	dog#2	dog#3	mean±SD
T _{max} (h)	0.5	0.75	1.0	0.75±0.25
C _{max} (ng/ml)	340.2	243.4	156.8	246.8±91.74
AUC ₀₋₂₄ (ng·h/ml)	1124	2220	980	1441±678

1 SUMMARY

A pilot study was performed in which we attempted to quantify glatiramer acetate in human sera after subcutaneous (s.c.) administration of a 60 mg dose, i.e. three times the therapeutic dose, to healthy volunteers. Glatiramer acetate concentration in serum was determined by an enzyme-linked immunosorbent assay (ELISA). The study results showed that the available ELISA is not sufficiently sensitive to measure the anticipated levels of glatiramer acetate following the administration of the therapeutic dose.

2 STUDY DESIGN

The pharmacokinetic (PK) study was performed in 30 healthy male volunteers. The outline of the study design is summarized in Table 1.

Table 1: Study Design

Day 1	1) Drawing 10 mL of blood from each subject (pre-dosing) 2) S.C Injection of placebo (40 mg mannitol) to all subjects
Day 2	S.C injection of 20 mg Copaxone® or placebo.
Day 3	S.C injection of 40 mg Copaxone® or placebo.
Day 4	1) Drawing 10 mL of blood from each subject (clearance control). 2) S.C injection of 60 mg Copaxone® or placebo. 3) PK study:

Twenty subjects received Copaxone® and ten received placebo. The levels of glatiramer acetate were measured in the serum of seventeen subjects given Copaxone®.

The subjects received three successive single administrations of Copaxone® at doses of 20, 40 and 60 mg or placebo, by a subcutaneous injection, 24 hours apart. Blood samples were collected for PK analysis at 5, 15, 30, 60, 120, 240, and 360 minutes following the last injection.

Glatiramer acetate concentration in the serum samples was determined according to the ELISA Method SI-15566, attached to this report, with minor modifications.

3 RESULTS

The PK results from all subjects are summarized in Table 2.

Table 2: PK Results from 17 Healthy Volunteers after Receiving a 60 mg Dose of Copaxone® Subcutaneously

Subject#	LLOQ	T _{max} (min)	C _{max} (ng/mL)	AUC ₀₋₆ ⁽¹⁾ (min x ng/mL)	Second peak (min)
103 ⁽¹⁾	50	15	605	67532	360
105	25	15	69	2325	NQ
106	50	NQ ⁽²⁾	NQ	NQ	NQ
108	50	15	104	2334	NQ
111	25	30	126	4474	NQ
112	50	15	301	11358	360
113	25	30	76	1719	NQ
114	25	NQ	NQ	NQ	NQ
116	25	15 ; 240	114 ; 114	37267	240
119	25	30	77	5758	360
120	25	15	88	1644	NQ
121	50	NQ	NQ	NQ	NQ
123	25	NQ	NQ	NQ	NQ
124	50	NQ	NQ	NQ	NQ
126	25	NQ	NQ	NQ	NQ
127	25	NQ	NQ	NQ	NQ
130	25	NQ	NQ	NQ	NQ

1. The AUC₀₋₆ was calculated by the trapezoidal formula. All samples having glatiramer acetate concentration below the LLOQ (as determined for each patient) were considered as negative - "zero" glatiramer acetate.

2. NQ; Not Quantifiable.

Glatiramer acetate could be quantitatively detected in nine out of the 17 subjects who received Copaxone®. In all of these subjects, the T_{max} was between 15 and [] minutes, except for one subject who had an additional maximum peak at 240 minutes. This volunteer was also exceptional in that glatiramer acetate could be quantitatively measured in all his PK samples, including the "clearance control" sample (serum Day 4).

In seven out of the nine positive subjects the C_{max} was in the range of 69-126 ng/mL (mean ± CV% : 93 ng/mL ± 23%). In the other two subjects the C_{max} levels of glatiramer acetate were much higher (605 and 301 ng/mL, respectively).

The area under the curve (AUC) in the nine "positive" subjects exhibited a large variability, ranging from 1644 to 67532 min x ng/ml.

In all the positive subjects, glatiramer acetate levels returned to baseline within 30-60 minutes post injection. However, in four subjects quantifiable amounts of glatiramer acetate appeared again in the serum at a later time point of 240 or 360 minutes.

Glatiramer acetate could not be detected after 24 hours in samples of 15 out of the 17 subjects, indicating that 24 hours after the injection of the 60 mg dose, the levels of the immunorecognizable glatiramer acetate fragments in the serum of most subjects were below the quantitation limits (25-50 ng/mL).

4 CONCLUSIONS

- ▶ The results of this study reveal that the currently available ELISA method is not sensitive enough in order to reliably quantify the serum levels of glatiramer acetate following the administration of the therapeutic dose (20 mg).
- ▶ Notwithstanding, the results obtained in this pilot study confirm previous results in animals, in which radio-labeled drug was used, as well as studies performed in animals using a similar ELISA, in that glatiramer acetate has been found to be rapidly absorbed from the site of injection and rapidly removed from the circulation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-622/S-015

ADMINISTRATIVE and
CORRESPONDENCE DOCUMENTS



NDA 20-622

TEVA Pharmaceuticals USA
Attention: Scott Grossman
Director, Regulatory Affairs
1090 Horsham Road
North Wales, PA 19454

Dear Dr. Grossman:

Please refer to the meeting between representatives of your firm and FDA on April 3, 2001. The purpose of the meeting was to respond to Dr. Grossman's voice message left for Dr. Katz, containing questions about several different topics involving Copaxone Injection.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECON

DATE: April 3, 2001

APPLICATION NUMBER: 20-622/S015 Copaxone Injection

BETWEEN:

Name: Dr. Scott Grossman
Phone: (215) 591-8526
Representing: TEVA Pharmaceuticals USA

AND

Name: Dr. Russell Katz – Division Director
Dr. John Feeney – Group Leader
Dr. Armando Oliva – Group Leader
Dr. Gerald Tremblay – Medical Reviewer
Dr. Maryla Guzewska – CMC Team Leader
Teresa Wheelous, Regulatory Management Officer

SUBJECT: Division's response to a voice message left for Dr. Katz by Dr. Grossman, which contains questions involving several different topics about Copaxone Injection.

DISCUSSION:

Question 1 Can the MRI data be included in labeling?

•

• Only the primary outcome measure will be described in labeling.

• TEVA has the choice of accepting the division's labeling or may submit a counter proposal]

Question 2 Since TEVA has agreed to our version of labeling can they receive an earlier due date than 6 months?]

• The official due date for this type of submission, a resubmission to a labeling supplement, is 6 months from the day of receipt. While the official date can not be changed, we are already close to sending an action; therefore, the full 6 months will not be needed.

• However, if TEVA chooses to submit a counter proposal for then the review period will be longer than if TEVA agrees to the division's labeling]
]

- Dr. Grossman will get back to the division with TEVA's decision regarding the inclusion of MRI data in labeling.

Question 3 Do we accept documents in the format of the common technical document?

- The Agency does not yet have an official position regarding the acceptance of the common technical document format, but the division is willing to accept the common technical format.

Question 4 []

[]

[

]

Informed Consent Point of Clarification

- Once a drug is approved in Canada it is available for consumer purchase, even though the drug product may be undergoing the provincial funding process.

ACTION ITEMS

1. Dr. Grossman will get back to the division about TEVA's position on the inclusion of MRI data in labeling.
2. The division will get back to TEVA in a couple of weeks about its position on the Informed Consent issues mentioned in the approvable letter of Jan. 19, 2001.
3. Further discussions will be arranged pending the outcome of action items #1 and #2 stated above.

Russell Katz, M.D.
Division Director
Teresa Wheelous, Regulatory Management Officer

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

/s/

Teresa Wheelous
5/4/01 03:22:47 PM
CSO
Russell Katz
5/8/01 11:22:35 AM
MEDICAL OFFICER

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

/s/

Teresa Wheelous
5/8/01 03:27:19 PM
Teresa Wheelous [for John Purvis]



NDA 20-622/S-015

TEVA Pharmaceuticals USA
Attention: Scott Grossman, Ph.D.
Director, Regulatory Affairs
1090 Horsham Road
North Wales, PA 19454-1090

Dear Dr. Grossman:

We acknowledge receipt on March 19, 2001 of your March 16, 2001 resubmission to your supplemental new drug application for Copaxone (glatiramer acetate) for Injection.

This resubmission contains additional labeling revision and clinical trial conduction information submitted in response to our January 19, 2001 action letter.

With this amendment, we have received a complete response to our January 19, 2001 action letter.

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Jack Purvis

4/20/01 09:46:16 AM



ORIGINAL

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Scott L. Grossman, Ph.D.
Director, Regulatory Affairs

Phone: (215) 591 3000
FAX: (215) 591 8600

Phone: (215) 591 8526
FAX: (215) 591 8820
scott.grossman@tevausa.com

NAT
NDA SUPPLEMENT

March 16, 2001

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Document Control Room (HFD-120)
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

MAR 19 2001

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NDA # 20-622
Copaxone® (glatiramer acetate for injection)
Response to Approvable Letter

NDA SUPP AMEND

AZ
SLR-015-BZ

Dear Dr. Katz:

This letter is to serve as an official response to the approvable letter received on January 19, 2001, regarding the pending labeling supplement S-015 originally submitted on August 4, 1999 and amended on April 20, 2000, October 11, 2000, October 16, 2000, November 14, 2000, November 21, 2000, and January 5, 2001.

We have included in this package a response to all issues raised by the Agency in the approvable letter. We believe we have addressed each issue thoroughly. Included in this package you will find the following:

- Tabs 1 through 3: Teva responses to FDA statements regarding the conduct of the clinical trials
- Tabs 4 through 7: Teva responses to labeling issues including revised draft labeling
- Tab 8: Teva response to additional safety or efficacy request

If you have any questions or require additional information, please do not hesitate to call me at 215-591-8526. Thank you.

Sincerely,

Scott L. Grossman
Scott L. Grossman, Ph.D.,
Director, Regulatory Affairs



DUPLICATE

*Jellison in DFS
1-31-01*

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

CENTER FOR DRUG EVALUATION
AND RESEARCH

Scott L. Grossman, Ph.D.
Director, Regulatory Affairs

Phone: (215) 591 3000
FAX: (215) 591 8600

JAN 24 2001

Phone: (215) 591 8526
FAX: (215) 591 8820
scott.grossman@tevausa.com

RECEIVED HFD-120

January 23, 2001

NEW CORRESP
SLR-015(C)

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Document Control Room (HFD-120)
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

NDA # 20-622
Copaxone® (glatiramer acetate for injection)
Response to Approvable Letter

Dear Dr. Katz:

This letter is to serve as an official response to the approvable letter received on January 19, 2001, regarding the pending labeling supplement S-015 originally submitted on August 4, 1999 and amended on April 20, 2000, October 11, 2000, October 16, 2000, November 14, 2000, November 21, 2000, and January 5, 2001.

We have reviewed the Agency's concerns contained in the approvable letter and feel that we can come to an agreement regarding these areas and therefore, pursuant to 21 CFR 314.110, formally respond with our intent to file an amendment. As this supplement is of importance to our business, we will do our best to file a response as soon as possible thus allowing an extension of 45 days for your review period from date of receipt.

If you have any questions or require additional information, please do not hesitate to call me at 215-591-8526. Thank you.

Sincerely,

Scott L. Grossman, Ph.D.,
Director, Regulatory Affairs



Corporate Headquarters:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

January 5, 2001

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Document Control Room (HFD-120)
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

NDA # 20-622
Copaxone® (glatiramer acetate for injection)
Response to FDA Request for Information

Dear Dr. Katz:

This letter is to serve as an official response to the FDA Request for information regarding the pending labeling supplement S-015 originally submitted on August 4, 1999 and amended on April 20, 2000, October 11, 2000, and November 14, 2000.

Please find enclosed in this package the responses for two facsimiles received on December 22, 2000. The original questions are followed by the Teva answer.

If you have any questions or require additional information, please do not hesitate to call me at 215-591-8526. Thank you.

Sincerely,

Scott L. Grossman, Ph.D.,
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION
AND RESEARCH

JAN - 8 2001

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ORIGINAL
NDA SUPP AMEND

SLR-015 BM

/s/

Russell Katz
12/7/00 01:19:11 PM

**MEMORANDUM OF TELEPHONE CONVERSATION
NDA # 20-622/S-015**

Drug: Copaxone (glatiramer acetate) for Injection
Sponsor: TEVA
Date: November 15, 2000
Purpose: Information Request

ATTENDEES

FDA

Dr. J. Feeney – Group Leader
Dr. G. Tremblay – Medical Reviewer
T. Wheelous – Project Manager

TEVA

Linda Knapp – Regulatory Affairs

Discussion:

During the review of S-015 by the medical reviewer, questions regarding the informed consent used during the conduction of study #9003 (MRI) surfaced. The following information was requested:

1. Informed consent forms are located in volume 4 of the 18 volume August 1999 submission. Among these consent forms are Canadian forms dated January 1997 do not mention that Copaxone was approved in Canada in September 1997. Since the trial was ongoing after the approval of Copaxone, was the informed consent revised to reflect this new approval?
2. Within the informed consent forms there are statement regarding currently approved products for multiple sclerosis, e.g., Betaserone and Avonex, but not Copaxone. In the U.S. Copaxone was approved in December 1996 were patients notified of this approval?
3. Please provide copies of the inform consent revisions.

Since this information should be provided as soon as possible Ms. Knapp agreed to respond to the divisions information request on Monday, November 20, 2000.

cc: Orig IND
HFD-120
Feeney
Trembley
Wheelous

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MAY PROCEED TELECON

/s/

Teresa Wheelous
11/21/00 08:54:19 AM

**MEMORANDUM OF TELEPHONE CONVERSATION
NDA 20-622/S-015**

Drug: Copaxone Injection
Sponsor: TEVA Pharmaceuticals
Date: October 27, 2000
Conversation Between:

<u>Agency:</u>	<u>Sponsor:</u>
Dr. R. Katz – Division Director	W. Mulcahy
Dr. J. Feeney – Group Leader	M. Nicholas – Aventis, Reg. Affairs
Dr. G. Trembley – Medical Reviewer	M. Hershkowitz – Reg. Affairs
Ms. T. Wheelous – Project Manager	S. Grossman – Reg. Affairs

Purpose: To inform TEVA of the division's projected goal date for action on 20-622/S-015.

Discussion:

1. Goal Date

- At the request of TEVA to receive a firm goal date, the division has decided to issue an action letter by mid January 2001.

2. Submitting Additional Information during Review Cycle

- TEVA inquired about the possible effect on the due date if additional information regarding is submitted during this review period. This new data is obtained from
- The final report for study 9003 was recently submitted.
- If additional data are submitted within the next two weeks, then the goal date will not be altered. However, the division does not know if the additional data will help to support the proposed claims.

3. TEVA's Request to Meet During the Review Cycle

- TEVA has offered to assist in the review process by meeting with the division and present the data and rationale for the claims offered in labeling.
- This sort of meeting is not ordinarily helpful during the review process, but rather tends to slow the review process. The preference is to allow the division to review the application, and then meet if needed.
- However, if during the review cycle and after internal discussions, the division feels that a meeting is needed TEVA will be contacted to arrange a date and time to meet.

- TEVA believes that a meeting during the review cycle will provide an opportunity to present a comprehensive argument in support of the proposed claims. If TEVA feels that the application does not adequately present a comprehensive argument, then it is suggested that a written comprehensive argument be submitted to the file without resulting in an extension of the review period.

4. Administrative Procedures

- TEVA was reminded that all direct administrative questions (e.g., meeting requests, due dates, etc.) should be relayed to the division through the project manager and not asked of the reviewer.

cc: Orig IND
HFD-120

/Katz
/Feeney
/Tremblay
/Wheelous

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TELECON

/s/

Russell Katz
11/21/00 03:22:14 PM



NDA 20-622/S015

INFORMATION PROVIDED LETTER

TEVA Pharmaceuticals USA
Attention: Scott Grossman, Ph.D.
Director, Regulatory Affairs
1510 Delp Drive
Kulpsville, PA 19443

Dear Dr. Grossman:

Please refer to your supplemental new drug applications S-015 dated August 5, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Copaxone (glatiramer acetate) for Injection 20mg/vial.

We also refer to an October 27, 2000, telecon between representatives of this Division and several TEVA representatives.

In that telephone conversation we agreed to provide TEVA with a written goal date for this application. This letter serves to inform you that the goal date, as discussed in the telecon, for this application is January 16, 2001.

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

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

NDA 20-622/S-015

Page 3

Cc:

Division File

HFD-120

/Katz

/Feeney

/Trembley

/Wheelous

Draft: November 1, 2000 & November 21, 2000

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INFORMATION PROVIDED LETTER

/s/

Russell Katz
11/21/00 03:17:22 PM



ORIGINAL

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Scott L. Grossman, Ph.D.
Director, Regulatory Affairs

Phone: (215) 591 3000
FAX: (215) 591 8600

Phone: (215) 591 8526
FAX: (215) 591 8820
scott.grossman@tevausa.com

November 14, 2000

CENTER FOR DRUG EVALUATION
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NOV 15 2000

RECEIVED HFD-120

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Document Control Room (HFD-120)
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

NDA SUPPLEMENT
(BL)
SLR-015

NDA # 20-622
Copaxone® (glatiramer acetate for injection)
Re: Amendment to a Pending Application, S-015

Dear Dr. Katz:

Pursuant to our conversation on October 27, 2000 please find attached an amendment to the above pending labeling supplement. As we had discussed, this amendment contains data that increases the duration of open label efficacy data from six years to at least seven years in 69 patients. It is our understanding from our conversation that this amendment will not change the Division review goal date of January 2001.

Please find enclosed:
FDA Form 356H
Annotated labeling
Clean copy labeling
List of annotations for the labeling
7-Year Cohort Report, including Protocol

If you have any questions or require additional information regarding the above, please do not hesitate to call me at 215-591-8526. Thank you.

Sincerely,

Scott L. Grossman, Ph.D.,
Director, Regulatory Affairs

ORIGINAL

**MEMORANDUM OF TELEPHONE CONVERSATION
NDA 20-622/S-015**

Drug: Copaxone Injection
Sponsor: TEVA Pharmaceuticals
Date: October 11, 2000
Conversation Between:

Agency:
Dr. G. Tremblay – Medical Reviewer
Ms. T. Wheelous – Project Manager

Sponsor:
M. Hershkowitz – Reg. Affairs
W. Mulcahy
Dr. Smadar
S. Grossman – Reg. Affairs

Purpose: To repeat the clinical request information necessary to expedite the review of 20-622/S-015.

Background:

This application was submitted to the Agency in August of 1999 and is under review. A new medical reviewer, Dr. Tremblay, was recently assigned to review the application. During his review of the September 15, 2000 labeling comparison of the proposed S-015 vs. the last approved label of April 2000 for S-004 and S-007, Dr. Tremblay was unable to locate annotations listed in this document comparison nor attachments mentioned in the April 20, 2000 amendment to this application. Since Dr. Grossman did not clearly understand the information request that I left him in a voice message on Oct. 2, 2000, a telecon was arranged with Dr. Grossman, Dr. Tremblay, and myself.

Discussion:

Upon calling Dr. Grossman at the agreed upon time, Dr. Tremblay and I were informed that there would be several additional participants in the telecon. I reminded Dr. Grossman that this was to be an information request telecon and that Dr. Tremblay was participating in effort to clarify the clinical information request made earlier.

1. Request for a List of Annotations

- Dr. Tremblay noted that the recent September 15, 2000 labeling comparison contains additional annotations that were not provided in earlier labeling comparisons.
- A copy of the proposed labeling along with all of the annotations together in one document was requested.
- TEVA stated that in addition to the August 4, 1999 submission and the April 20, 2000 amendment, this supplement requires review of a submission made to an earlier supplement.
- The submission dated June 1999 contains safety data, including some attachments, for clinical trial #9003.

2. Request for Attachments and Amendments to Protocol for Study#9003

- Dr. Tremblay requested a copy of the protocol and all of its amendments for study #9003.
- The April 20, 2000 submission refers to an attachment #14, but this attachment can not be readily located.
- Please provide either the location of the attachments or a copy of all of the attachments for both study #9001 and study #9003.

3. Submission of Additional amendments to S-015

- TEVA would like to submit the final study report to supplement the draft report submitted in April 2000.
- TEVA inquired about the likelihood of an altered action date if the final report is submitted now. Dr. Tremblay reminded TEVA that he was not in the position to make this decision and that this type of decision is the Division director's call.

4. Additional TEVA Requests

- TEVA offered review assistance to Dr. Tremblay, who referred TEVA to the Division director for a reply to their offer.
- TEVA also requested a written statement from the division regarding the goal date for an action on this application.
- Lastly, TEVA requested to reschedule the October 23, 2000 telecon.

Orig NDA 20-622
HFD-120

/Katz
/Feeney
/Tremblay
/Wheelous

Draft: November 7, 2000
C:\wheelous\nda\copaxone\101100tel.doc

TELECON

/s/

Teresa Wheelous
11/9/00 02:06:12 PM
CSO



ORIGINAL

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Scott L. Grossman, Ph.D.
Director, Regulatory Affairs

Phone: (215) 591 3000
FAX: (215) 591 8600

Phone: (215) 591 8526
FAX: (215) 591 8820
scott.grossman@tevausa.com

CENTER FOR DRUG EVALUATION
AND RESEARCH

OCT 17 2000

RECEIVED HFD-120

October 16, 2000

Teresa Wheelous, R.Ph.
Division of Neuropharmacological Drug Products
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

NDA SUPP AMEND

SLR-015-Bh

NDA # 20-622
Copaxone® (glatiramer acetate for injection)
Response for Information: FDA Correspondence

Dear Ms. Wheelous:

Per your October 10, 2000, request for information, enclosed is the annotated draft proposed label (dated 9/15/00) as well as the reports and published literature cited in the draft annotated label. We hope that the medical reviewer will find these helpful in reviewing the submission.

If you have any questions regarding the enclosed information, please contact me at 215-591-8526.

Sincerely,

Scott L. Grossman, Ph.D.
Director, Regulatory Affairs



ORIGINAL

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Scott L. Grossman, Ph.D.
Director, Regulatory Affairs

Phone: (215) 591 3000
FAX: (215) 591 8600

Phone: (215) 591 8526
FAX: (215) 591 8820
scott.grossman@tevausa.com

CENTER FOR DRUG EVALUATION
AND RESEARCH

October 11, 2000

OCT 12 2000

RECEIVED HFD-120

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Document Control Room (HFD-120)
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

NDA SUPP AMEND

SLR-015-BM

NDA # 20-622

Copaxone® (glatiramer acetate for injection)

Re: Final Clinical Trial Report, Amendment to a Pending Application, S-015

Dear Dr. Katz:

Reference is made to the New Drug Application (NDA) for Copaxone® (glatiramer acetate for injection), originally submitted on June 15, 1995 and approved on December 20, 1996. Copaxone® is provided in lyophilized form to be reconstituted with sterile water diluent prior to subcutaneous injection in the treatment of relapsing-remitting multiple sclerosis. The purpose of this communication is to provide a final Clinical Trial Report containing open-label information for Protocol 9003, entitled A Multi-National, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study, Extended by Open-Label Treatment, to Study the Effect of Copaxone® (Copolymer-1) on Disease Activity as Measured by Cerebral Magnetic Resonance Imaging in Patients with Relapsing-Remitting Multiple Sclerosis.

The original clinical trial report was submitted June 8, 1999 (S-009). Revised labeling which accounted for the addition of MRI data was filed August 4, 1999 (S-015). Later, on April 20, 2000, the S-015 submission was amended with a summary report describing the MRI data from the open label extension of Study 9003. The enclosed final Clinical Trial Report in this submission replaces the summary in S-015.

If you have any questions or require additional information regarding the above, please do not hesitate to call me at 215-591-8526. Thank you.

Sincerely,


Scott L. Grossman, Ph.D.,
Director, Regulatory Affairs



Scott L. Grossman, Ph.D.
Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road
PO BOX 904
Sellersville, PA 18960

ORIGINAL

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive
PO BOX 247
Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

NDA SUPP AMEND

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-6352

SLR-015 (BL)

April 20, 2000

CENTER FOR DRUG EVALUATION
AND RESEARCH

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Document Control Room (HFD-120)
Food and Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

APR 21 2000

RECEIVED HFD-120

Re: NDA 20-622
Copaxone (glatiramer acetate for injection)
Amendment to Labeling Supplement (Submitted on August 04, 1999)

Dear Dr. Katz:

Reference is made to the New Drug Application cited above, originally submitted on 13 June 1995 and approved on 20 December 1996. Pursuant to the telephone conference call which took place on December 15, 1999 between Ms. Teresa Wheelous, R.Ph. and Scott Grossman, Ph.D., the purpose of this correspondence is to submit revised labeling for the above-referenced product as an amendment to the Labeling Supplement filed on August 04, 1999. As discussed in the December 15, 1999 teleconference and confirmed on April 17, 2000 we are making this submission with the understanding that it will not increase the time allotted for review of the August 04, 1999 Labeling Supplement submission.

This submission contains draft labeling and the supporting documentation "Protocol 9003, Long-Term MRI Data Summary Report". This summary report includes data from the open-label active phase of study 9003 entitled "A Multi-National, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study, Extended by Open-Label Treatment, to Study the Effect of Copaxone® (Copolymer-1) on Disease Activity as Measured by Cerebral Magnetic Resonance Imaging in Patients with Relapsing-Remitting Multiple Sclerosis". Data from the 9 month double-blind portion of the study were submitted in the August 04, 1999 supplement.

Based upon information derived from the open-label data submitted in this amendment, changes in the labeling have been made in the following sections: CLINICAL PHARMACOLOGY (Clinical Trials), and INDICATIONS AND USAGE.

The annotated labeling included herein is intended to replace the previously submitted version (Rev. P/99). Version P/99 was originally included in the Labeling Supplement submitted in eight (8) volumes on August 04, 1999. The draft labeling included herein does not include changes proposed by the FDA as a result of the review of S-004 and S-009 and received by Teva via fax on April 17, 2000.

In support of this amendment, please find attached the following:

Attachment 1: Four (4) copies of the draft package insert labeling, (Rev. 4/18/00 DRAFT)

Attachment 2: Annotated Version Compare (Rev. 4/18/00)

Attachment 3: Copaxone, Protocol 9003, Long-Term MRI Data, Summary Report

Should you have further questions, please do not hesitate to contact the undersigned.

Sincerely,

A handwritten signature in cursive script that reads "Scott L. Grossman".

Scott L. Grossman, Ph.D.
Director, Regulatory Affairs



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpville, PA 19443

Phone: (215) 256 8400
FAX: (215) 721 9669

Toll Free: (888) TEVA USA
FAX: (215) 256 7855

4 August 1999

ORIGINAL

**CENTER FOR DRUG EVALUATION
AND RESEARCH**

AUG 05 1999

RECEIVED HFD-120

Russell Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products
Document Control Room (HFD-120)
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

PRIOR-APPROVAL SUPPLEMENT

NDA 20-622
Copaxone® (glatiramer acetate for injection)
Supplement – Labeling Supplement

NDA NO. 20-622 REF NO. SLR-015
NDA SUPPL FOR Labeling

Dear Dr. Katz,

Reference is made to the New Drug Application cited above, originally submitted on 13 June 1995 and approved on 20 December 1996. Pursuant to 21 CFR 314.70(b)(3) the purpose of this correspondence is to submit revised labeling for the above-referenced product. Based upon information derived from clinical as well as non-clinical studies completed after market approval, changes have been made to the following sections: CLINICAL PHARMACOLOGY (Mechanism of Action, Pharmacokinetics, and Clinical Trials), INDICATIONS AND USAGE, PRECAUTIONS (Considerations Regarding the Use of a Product Capable of Modifying Immune Responses, Drug Interactions, and Carcinogenesis, Mutagenesis, Impairment of Fertility), and ADVERSE REACTIONS (Chest Pain). In addition, minor editorial changes have been made throughout the labeling.

Statistics employed in the proposed labeling include both ANOVA and ANCOVA. Specifically, we have expressed the number of relapses from study as the baseline-adjusted mean along with the corresponding p-value obtained using the ANOVA. This was done in order to maintain the same concept and format employed in the currently approved labeling.

In support of this supplement please find attached four copies of draft package insert labeling as well as an electronic comparison document of the proposed labeling with labeling submitted to the Division on 8 June 1999 as a Special Supplement – Changes Being Effected. This comparison document is fully annotated to facilitate your review.

Please note that glatiramer acetate was formerly known as Copolymer-1. Should you have any questions or require further information, please do not hesitate to contact Scott L. Grossman, Ph.D., Director, Regulatory Affairs or the undersigned.

Sincerely,



Kathleen F. Dusek, R.Ph., RAC
Senior Regulatory Affairs Associate

Attachments