

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-724

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20855

CLINICAL INSPECTION SUMMARY

DATE: June 30, 2004

TO: Jackie Ware, Pharm.D., Senior Regulatory Project Manager
Howard Chazin, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-724

APPLICANT: Pfizer

DRUG: Pregabalin

THERAPEUTIC CLASSIFICATION: Type S

PROPOSED INDICATION: Adjunctive therapy in the treatment of partial seizures

CONSULTATION REQUEST DATE: December 16, 2003

ACTION GOAL DATE: August 31, 2004

I. BACKGROUND:

LyricaTM(pregabalin), CI-1008, is an analogue of the neurotransmitter gamma-aminobutyric acid (GABA). The mechanism of action of pregabalin is selective binding to the alpha₂-delta protein and the resulting decrease in neurotransmitter release. In this NDA application, the sponsor has requested the use of pregabalin as adjunctive therapy in the treatment of partial seizures

The application included the results from the pivotal protocols 1008-009 entitled "Pregabalin Add-On Trial: A Double-Blind, Placebo-Controlled, Multicenter Study in Patients with Partial Seizures", and 1008-034 entitled "Pregabalin BID Add-On Trial: A Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study in Patients with Partial Seizures."

Protocol 1008-009

The study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in men or women 18 years of age or older with a body weight of at least 50 Kg, diagnosed with partial seizures. These subjects must have failed to have adequate seizure control with standard antiepileptic drugs (AEDs) and on at least 1 but not more than 3 AEDs at doses within an acceptable therapeutic range. The study comprised of an 8-week baseline phase with at least 6 partial seizures and no 4-week seizure-free period. The patients were then randomized to parallel treatment groups: 200 mg tid, 300 mg bid (blinded using tid dosing), or placebo in addition to their concurrent AED therapy for the 12-week double-blind treatment including a 7-day study drug titration. For those patients choosing to exit the study, the study consisted of a double-blind withdrawal phase. Those patients choosing to continue the open-label pregabalin treatment were enrolled in a follow up study (protocol 1008-10). The primary endpoint, response ratio (RRatio or symmetrized percent change for all partial seizures), was a comparison of baseline seizure frequency with treatment partial seizure frequency (week 20/termination). This was calculated utilizing the patient's seizure data by dividing the difference between 28-day seizure rates during treatment and baseline by the sum of baseline and double blind seizure rates.

Protocol 1008-034

The study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in men or women 12 years of age or older with a body weight of at least 40 Kg (88 lb), diagnosed with partial seizures. These subjects must have failed to have adequate seizure control with standard antiepileptic drugs (AEDs) and on at least 1 but not more than 3 AEDs at doses within an acceptable therapeutic range. The study comprised of an 8-week baseline phase with at least 6 partial seizures and no 4-week seizure-free period. The patients were then randomized to parallel treatment groups: 50, 150, 300 or 600 mg/day administered bid dosing or placebo in addition to their concurrent AED therapy for the 12-week double-blind treatment. For those patients choosing to exit the study, the study consisted of a 6-day double-blind withdrawal phase. Those patients choosing to continue the open-label pregabalin treatment were enrolled in a follow up study (protocol 1008-35). The primary endpoint, response ratio (RRatio or symmetrized percent change for all partial seizures), was a comparison of baseline seizure frequency with treatment partial seizure frequency. This was calculated utilizing the patient's seizure data by dividing the difference between 28-day seizure rates during treatment and baseline by the sum of baseline and double blind seizure rates.

Inspection assignment was issued in January 2004 for three domestic sites: _____
_____ for protocol 1008-009 and _____ for inspection of his conduct in protocol 1008-034. These investigators enrolled a large number of subjects and contributed significant results.

II. RESULTS (by site):

NAME	Protocol (Site #)	Location	ASSIGNED DATE	DATE EIR RECEIVED	CLASSIFICATION
L	1008-009 (site 4)	New York, NY	01/12/2004	03/22/2004	NAI
	1008-009 (site 45)	Gainesville, FL	01/12/2004	03/22/2004	VAI
	1008-034 (site 21)	Asheville, NC	01/12/2004	05/09/2003	NAI

1. (Protocol 1008-009; Site 4)

- a. What was inspected: At this site, 14 subjects were enrolled in protocol 1008-009. An audit was done on source records from 5 subjects (4002, 4003, 4004, 4011 and 4012). Inspection reviewed the source documents, CRFs and compared with data listing (primary efficacy and adverse events) provided by the sponsor as part of the NDA submission.
- b. Limitations of inspection: N/A.
- c. General observations/commentary:

According to the establishment inspection report, there was adequate documentation to ensure that all audited subjects did exist, met eligibility criteria and were available for the duration of their stated participation in the study. All subjects signed the informed consent. The FDA investigator checked the baseline and double-blind seizure rates along with response ratios and percent changes and noted these values were accurately calculated and reported in the NDA for those 5 subjects reviewed. Clinical laboratory results, ECG and EEGs were available for review and on file. The site conducted ophthalmologic examinations required by the protocol and adverse event experiences reported for all 14 subjects.

No Form FDA-483 was issued at the end of inspection. However, the inspection revealed that the following adverse events reported by the site in the CRF were not listed in NDA adverse event data listing provided by the sponsor for the audit:

- 1) Subject 4005 experienced multiple episodes of tiredness, mild intensity, between . The investigator assessed it was related to study drug and subject recovered from this AE without any action taken on study drug dosage.
- 2) Subject 4012 had a single episode of mild GI upset started on and ended . This was not related to study drug and no action was taken regarding study drug dosage.

- d. Recommendation:

DSI would suggest the review division to check in the NDA data listing regarding the missing AE data at time points as stated for above 2 subjects and include these in safety evaluation. Overall, data appear acceptable.

2. _____ (Protocol 1008-009; Site 45)

a. What was inspected: 29 subjects were screened, 21 subjects were randomized at this site (site #45). 4 subjects were discontinued and 17 subjects completed the study. Reasons for discontinuation included adverse events for subject 006 and 014. An audit of 12 subjects' records was conducted. The FDA investigator reviewed the source documents, CRFs and compared with data listing (primary efficacy and adverse events) provided by the sponsor as part of the NDA submission.

b. Limitations of inspection: N/A.

c. General observations/commentary:

No Form FDA-483 was issued at the end of inspection. The discussion included:

- 1) Subject 10 had clinically significant levels of liver enzymes at double-blind (DB) visits 2 (_____), and 3 (_____): alkaline phosphatase 234 and 259 U/L (normal range 43-122 U/L), AST 183 and 80 U/L (15-46), ALT 108 and 48 U/L (11-66) respectively. The site referred the subject to see a specialist on 1/19/99. This was not reported in AE-CRF.
- 2) Prior to signing the informed consent by subject 004 on _____, the protocol required assessments such as EKG, EEG and X'Rays were performed on _____

The sponsor granted the site with several waivers. For example,

- 1) Abnormal ophthalmologic findings in subject 009, 025, 027
- 2) Abnormal laboratory results: abnormal neutrophils for subject 011 at baseline; wrong CBC report for subject 013 by _____; rechallenge drug following abnormal labs for subject 014.
- 3) Subject 007: compliance related to study drug
- 4) Subject 008: assessments (EKG; ophthalmologic exam) done after B1 visit
- 5) Subject 014: seizure classification
- 6) Subject 017: the minimum weight criteria.
- 7) Subject 022: study completion visit two weeks earlier to comply with sponsor's data entry due date

d. Recommendation:

DSI would suggest the review division to check in the database regarding above waivers and the elevated LFT experienced by subject 010 during the DB visits 2 and 3 and consider impact of some of these in clinical data review. Otherwise, data appear acceptable.

3. _____ (Protocol 1008-034; Site 21)

- a. What was inspected: For protocol 1008-034, 28 subjects were screened, five subjects were screen failures, five subjects were discontinued (#21001, 21014, 21016, 21025 and 21027) and 18 subjects completed the study. An audit of 10 subjects' records was conducted.
- b. Limitations of inspection: N/A.
- c. General observations/commentary: No major objectionable conditions noted following the review of the source documents, the CRF and data listing (primary efficacy and safety). No Form FDA-483 was issued. All subjects signed the informed consent.

Subject 21027 was hospitalized for aspiration pneumonia and this serious adverse event was reported by this site.
- d. Recommendation: Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the study sites that were inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted based on the limited numbers of the study subjects' records inspected except the missing AE data at time points as stated for 2 subjects at _____ site. DSI would suggest the review division to note several waivers granted by the sponsor for protocol violations and the elevated LFT experienced by subject 010 during the double blind visits at _____ site. Overall, data from these centers that had been inspected appear acceptable for use in support of this NDA.

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviations(s) from regulations. Data acceptable

VAI-RR= Deviation(s) form regulations, response received and reviewed. Data acceptable

OAI = Significant deviations for regulations. Data unreliable

cc:

NDA 21-724

HFD-45/Division File/Reading File

HFD-45/Program Management Staff (electronic copy)

HFD-46/U

HFD-46/Khin

HFD-46/George GCPB1 Files

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/s/

Ni Aye Khin
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MEDICAL OFFICER

Khin U
7/1/04 03:40:43 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Florian Zielinski, Ph.D., HFD - 357		FROM: Sharon Kelly, Ph.D., HFD - 170		
DATE Jan. 5, 2003	IND NO.	NDA NO. 21-724	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT Oct. 30, 2003
NAME OF DRUG Pregabalin	PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE February, 2004	
NAME OF FIRM: Pfizer, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please conduct an environmental assessment for NDA 21-724 Pregabalin. (s)-3-(aminomethyl)-5-methylhexanoic acid. This NME is also the subject of three additional NDA's, one Priority review 21-446 and two Standard review: NDA 21-723 ; 				
SIGNATURE OF REQUESTER Sharon Kelly, Ph.D. Chemistry Reviewer		METHOD OF DELIVERY (Check one) X MAIL		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Ravi Harapanhalli
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EA Consult

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 18, 2004
TIME: 3:30 – 5:30 pm
LOCATION: Parklawn Building, Potomac Conference Room
APPLICATION: 21-446
DRUG NAME: LYRICA (pregabalin) Capsules
TYPE OF MEETING: Type B, Post-action meeting

MEETING CHAIRS: Bob Meyer, MD and Robert Temple, MD

MEETING RECORDER: Lisa Malandro

FDA ATTENDEES:

HFD-170

Bob Meyer, MD	Director, Office of New Drugs II
Bob A. Rappaport, MD	Division Director
Celia Winchell, MD	Team Leader, Addiction Drug Products
Mwango Kashoki, MD, MPH	Medical Officer
Lisa Malandro	Regulatory Project Manager

HFD-550

Wiley Chambers, MD	Deputy Division Director
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HFD-120

Robert Temple, MD	Director, Office of New Drugs I
John Feeney, MD	Neurology Team Leader
Alice Hughes, MD	Safety Team Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Toni Hoover, PhD	Development Leader
Paul Nitschmann, MD	Regulatory
Jonathon Parker	Regulatory
Kathleen Dowd	Team Leader
Richard Kavoussi, MD	Clinical
Kevin Chartier, PhD	Statistics
Mark Pierce, MD	Clinical
Mitch Brigell, PhD	Clinical
	Consultant
	Consultant

BACKGROUND:

This meeting was a continuation of previous discussions regarding the ophthalmologic findings from clinical trials of pregabalin. Most recently, a teleconference (June 16, 2004) and a meeting (July 14, 2004) focused solely on these issues and resulted in the inability to come to agreement on the precautionary language in the label. Following receipt of an "approvable" action on July 26, 2004, Pfizer requested a post-action meeting to discuss the ophthalmologic data in more detail with appropriate representation from the Divisions and Offices involved in their four applications (NDA 21-446, 21-723, 21-724 and _____) in order to attempt to reach agreement on appropriate precautionary language in the label.

MEETING OBJECTIVES:

The purpose of the meeting was to review the ophthalmologic data in an attempt to reach agreement on interpretation of the ophthalmologic findings to allow for finalization of the label.

DISCUSSION POINTS:

The meeting began with a presentation of the history of Pfizer's conclusions regarding visual field and visual acuity testing. The slides that Pfizer presented are attached to these meeting minutes.

After review of the results from the controlled data, Pfizer discussed 10 cases that were of particular interest to them from the open-label experience. While no one case definition was applied to identify these 10 cases, it was clear from the discussion that at least some of the cases were identified because they experienced binasal field cuts, a pattern of field loss that has been linked in some reports to vigabatrin, a structurally similar drug.

While Pfizer maintained that the 10 cases of interest for the most part showed resolution of the field defects, Dr. Chambers believed the evidence for improvement was much less certain. In part, this was due to some inaccuracies in describing the evolution of the cases present in previous documents reviewed by Dr. Chambers. Nevertheless, Pfizer's representatives contended that similar cases probably existed in controlled trials for even the placebo-treated patients, and that the overall number of otherwise worrisome cases in the uncontrolled data was small. The cases from controlled experience lacked the longitudinal follow-up, however.

Pfizer's representatives stated that they had not identified a field loss in pregabalin-treated patients that exactly matched the field loss characteristic of vigabatrin. Pfizer acknowledged that the ten patients' fields were not all normal, but also stated that they were not definitively due to drug. Pfizer concluded that among the ten abnormal cases, there is no pattern or reason to believe a group of them had drug-related visual field defects.

Dr. Chambers stated that most of these cases did, in fact, become worse over time. Sometimes the pattern was different as it evolved, but clearly did not return to normal or sometimes even to baseline.

Dr. Chambers pointed out that overall the data collection was inadequate, that threshold testing should have been performed, and that follow-up was erratic. Some of the resolved visual field defects were collected after discontinuation of drug (in many cases 2.5 years following drug discontinuation) and we do not know what would have happened if drug had been continued.

In light of the results from controlled-trial experience, the attendees discussed briefly whether it was feasible and worthwhile to recommend monitoring for ophthalmologic changes. The "validated" data on visual fields was less impressive than the "all cases" analysis of visual fields. With respect to visual acuity, patients can tell if they are experiencing visual acuity changes, therefore, monitoring is not as necessary. Due to the variability of visual field testing, Pfizer expressed concern that slight variation in visual field tests would cause many pregabalin patients to stop taking a beneficial drug even though a similar percent of placebo patients would experience similar visual field defects. Pfizer is also concerned that the strong language proposed by the Agency would cause physicians and patients to compare the findings in pregabalin to those in vigabatrin.

During the discussion of the controlled data, it became clear that one of the epilepsy trials included in the pooled controlled trial data on visual fields incorporated only crude confrontational visual field testing and therefore should not be factored into the occurrence rate of visual field disturbances, as it adds no information to the numerator. There was general agreement that this data should not be pooled with the other visual field testing.

ACTION ITEM:

Drs. Meyer, Temple, and Chambers agreed to discuss and reconsider this information and to provide Pfizer with a recommendation for the precautionary language in the label.

FDA RECOMMENDATION FOLLOWING THE MEETING:

Drs. Meyer and Temple recommended that the most recent proposed precautionary wording from Pfizer was acceptable with two modifications:

1. The relative percent that was previously calculated based upon the number of validated cases should be re-calculated based upon the total number of cases.
2. The re-calculation of the relative percent also should not include the epilepsy study in which only confrontational visual field testing was performed.

This recommendation was communicated to Pfizer via telephone on Friday, August 20, 2004.

ATTACHMENT:

1. Slides presented by Pfizer at the meeting.

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-1

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/s/

Lisa Malandro
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MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 14, 2004
TIME: 1:30 pm
LOCATION: Parklawn Building, Conference Room C
APPLICATIONS: 21-446, 21-723, 21-724, 21-725
DRUG NAME: LYRICA (pregabalin) Capsules
TYPE OF MEETING: TYPE C

MEETING CHAIR: Wiley Chambers, MD

MEETING RECORDER: Lisa Malandro

FDA ATTENDEES: (Title and Office/Division)

Wiley Chambers, MD	Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (DAAODP)
William Boyd, MD	DAAODP
Celia Winchell, MD	Division of Anesthetic, Critical Care and Addiction Drug Products (DACCADP)
Mwango Kashoki, MD, MPH	DACCADP
Lisa Malandro	DACCADP

EXTERNAL CONSTITUENT ATTENDEES:

Jonathon Parker, RPh, MS	Regulatory
Betsy Garofalo, MD	Regulatory
Mitch Brigell, MD	Clinical
Rich Kavoussi, MD	Clinical

BACKGROUND:

This meeting was a continuation of previous discussions regarding the ophthalmologic findings from clinical trials of pregabalin. Most recently, a teleconference held on June 16, 2004, focused solely on these issues. No consensus regarding the labeling language was reached at the teleconference. Following additional revisions by the Sponsor, this face-to-face meeting was scheduled so that the ophthalmologic data could be discussed in more detail in order to attempt to reach agreement on appropriate precautionary language in the label.

MEETING OBJECTIVES:

The objective of this meeting was to discuss the ophthalmologic findings with regard to the labeling recommendations provided by the Agency to the Sponsor.

DISCUSSION POINTS:

Discussion focused on three ophthalmologic findings: blurred vision, visual field defects and loss of visual acuity.

Blurred Vision and Visual Acuity Changes:

The Sponsor agrees with the Division that there is a dose-related increase in incidence of both blurred vision and visual acuity changes. The Sponsor believes that blurred vision is a "CNS effect" that occurs early in treatment, and is related to dizziness and somnolence, other "CNS effects" of pregabalin. The Sponsor feels that this change is the same as any change caused by a sedating CNS drug. Consequently, The Sponsor suggested that blurred vision should be included in the label as an adverse event that patients reported, but not as an ophthalmologic effect of pregabalin, *per se*.

With respect to pregabalin's effect on visual acuity, the Sponsor stated that the changes noted in the randomized clinical trials were mostly mild, monocular changes with no progression or trend. In support of this description of the nature of the visual acuity changes, the Sponsor cited follow-up data from patients in the randomized trials who met the definition of a visual acuity "case" in which no significant change in acuity was observed. Based on the data, the Sponsor agreed that a description of the visual acuity changes should be included in the label.

Dr. Chambers responded that the test for visual acuity, the Snellen test, was inadequate to fully exclude that the blurred vision was not related to an effect on the optic nerve. Dr. Chambers also disagreed that concurrent dizziness and somnolence were sufficient to explain the reports of blurred vision. Dr. Chambers stated that overall, the ophthalmologic testing that was performed was inadequate to rule out an effect of pregabalin on vision. He explained that the Sponsor essentially conducted a "basic screening" of patients' vision. More appropriate evaluations should have included best corrected visual acuity testing and threshold testing for visual fields with repeat testing for patients who were dizzy or somnolent. Also, there were errors in data collection. However, despite the inadequacy of the ophthalmologic evaluations, adverse findings were noted and need to be investigated further.

Visual Field:

The Sponsor stated that data from the controlled trials did not show a dose-related change in visual fields, based on "validated cases," meaning cases which were detected in screening and then independently reviewed by ophthalmologists. In a comparison of validated cases of visual field defects (pregabalin vs. placebo), the Sponsor found that only the odds ratio of pregabalin 300 mg/d vs. placebo reached statistical significance. When a similar comparison was conducted using data from just the population of patients with pain due to diabetic peripheral neuropathy (DPN), there was no evidence that treatment with pregabalin was associated with a higher risk of visual field defects, including the 300 mg/d dose. The Sponsor is of the opinion that the lack of a dose effect or a pattern of visual field changes across treatment groups means that the increased risk noted for the 300 mg/d group is a chance finding, without any clinical significance. The Sponsor also expressed that the methods used were intentionally designed to "cast a wide net," and to pick up all cases, even those of questionable significance, and that the validation procedure was intended to identify cases which were truly of concern. The majority of cases seen, it

was noted, involved scattered loss of a few points at the periphery, which is distinctly different from the visual field loss seen in association with vigabatrin. The Sponsor expressed concern that including a labeling statement about visual field loss would confuse practitioners, who would falsely associate pregabalin with the types of visual field changes seen in patients treated with vigabatrin.

Dr Chambers responded that the numbers of patients in the controlled trials were too small to expect a statistically significant difference in individual groups; lack of significance is not a demonstration that the effect is ignorable. In fact, because of the small sample size and insensitive nature of the testing, the presence of any statistically significant differences at all is surprising and cause for concern. Dr. Chambers also stated that he noted an increase in the frequency of visual field defects for patients in all trials who were treated with 300 mg/d. This finding is a 'signal' indicating the need for further investigation, as is the high rate of visual field abnormalities noted from the screening evaluation that was conducted. Dr. Chambers noted that he had examined the cases and disagreed with the Sponsor regarding which were "explained" noting that he did not agree that the visual field defects had alternate explanations other than an effect of pregabalin.

The Sponsor pointed out the high rate of visual field defects in the placebo group, which Dr. Chambers suggested could be reflective of "noise" due to poor testing methods. The Sponsor argued that, given the high occurrence of visual field defects in both the placebo and pregabalin groups, it cannot be concluded that the data show a true effect of pregabalin on visual fields. Consequently, the current wording recommended by the Agency is problematic since the incidence of visual field defects is so high placebo patients.

The Sponsor also pointed out that the open-label treatment data do not show an increase in the occurrence of visual field changes over time, as might be expected with long-term exposure. The Sponsor believes that this supports the conclusion that the increased frequency of defects noted for the 300 mg/d group is a chance finding. Dr. Chambers reiterated his opinion that the increased frequency of events for that dose group is sufficient to suggest that there is a drug effect that needs to be included in the product label and followed up on in post-marketing studies. Dr. Chambers stated that threshold testing of visual fields, with follow-up that includes adequate testing methods, would be appropriate for further evaluation. Until such testing is completed and reviewed by the Agency, the current precaution in the label recommending visual field monitoring for all patients is appropriate. The Sponsor inquired whether Dr. Chambers would review additional statistical approaches to the data. Dr. Chambers expressed willingness to review additional materials, but also indicated doubt that the currently-available data would support any other interpretation than a need for further testing, with precautionary labeling in place until data support its removal.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

The precautionary language, regarding ophthalmologic effects of pregabalin, as proposed by the Agency, was not agreed upon at this meeting. The Sponsor was invited to submit alternative language that might assuage their concern regarding confusion with vigabatrin, but encouraged to retain the statements included in the most recent language proposed by the Agency.

ACTION ITEMS:

The Sponsor will provide the Division with revised language for an ophthalmologic precaution in the package insert.

ATTACHMENTS/HANDOUTS:

- Attachment 1: Handout provided by the Sponsor at the meeting.
- Attachment 2: Handout provided by Dr. Chambers following the meeting.
- Attachment 3: Revisions to the Precautions section submitted by the Sponsor on July 20, 2004

ATTACHMENT 1

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ATTACHMENT 2

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List of Questions for Requested Meeting to Discuss the Visual Field Data

1) Given the preponderance of evidence across indications and with doses higher and lower than 300 mg/day showing no signal of an adverse effect on visual fields with pregabalin, what causes the Division to conclude that the results with the 300 mg/day dose are anything other than a by chance finding due to multiplicity among numerous statistical analyses?

Response:

- The preponderance of evidence is that visual field defects were observed in the pregabalin clinical studies at a relatively high rate. The Summary of Visual Field Abnormalities from the MITT Population of Combined Controlled and Uncontrolled Studies reports a rate of 16.8% (582/3458). For a screening visual field test with a positive finding in every six people, it would seem prudent to recommend ophthalmological follow-up.*
- In controlled studies, the number of patients studied in each separate disease is too small to achieve sufficient power to detect statistically significant differences based on a screening test. Additionally, the doses studied for each indication are not exactly the same (300 mg was not studied in the anxiety indication.)*

	Placebo	P<300	300	450	600	Lorazepam	Placebo	P<300	300	450	600	Lorazepam	Placebo compar	300	600
Clinical	1062	772	523	197	769	109									
Ten or more miss	45	35	24	4	39	3	4%	5%	5%	2%	5%	3%			
Any VF	98	61	72	17	68	7	9%	8%	14%	9%	9%	6%			
	124	85	86	18	92	8	12%	11%	16%	9%	12%	7%			
Diabetic Neuropal	237	141	144		148										
7-8wk	14	7	5		10		6%	5%	3%		7%		2%	-1%	
	24	12	14		18		10%	9%	10%		12%		0%	-2%	
	31	18	17		24		13%	13%	12%		16%		1%	-3%	
Postherpetic Neu	163	153	25		56										
7-8wk	7	11	2		2		4%	7%	8%		4%		-4%	1%	
	24	16	6		8		15%	10%	24%		14%		-9%	0%	
	26	23	6		9		16%	15%	24%		16%		-8%	0%	
Chronic Pain	364	188	288	197	222										
8-12wk	12	2	10	4	13		3%	1%	3%	2%	6%		0%	-3%	
	30	15	47	17	25		8%	8%	16%	9%	11%		-8%	-3%	
	39	16	53	18	32		11%	9%	18%	9%	14%		-8%	-4%	
Epilepsy	141	122	66		191										
12wk	8	8	7		8		6%	7%	11%		4%		-5%	1%	
	7	12	5		9		5%	10%	8%		5%		-3%	0%	
	14	16	10		16		10%	13%	15%		8%		-5%	2%	
Anxiety	157	168			152	109									
5-12wk	4	7			6	3	3%	4%			4%	3%		-1%	
	13	6			8	7	8%	4%			5%	6%		3%	
	14	12			11	8	9%	7%			7%	7%		2%	

As seen in the table above, the percentage of patients with visual field findings was higher in the 300mg dose than in the placebo group for all indications where a comparison was made except

diabetic neuropathy. For the Diabetic Neuropathy group, the percentage difference was 1% and the 600mg dose had higher rates than placebo.

2) If the Division maintains that the 300 mg/day dose finding is of concern, then:

a) What is the specific pattern of visual field change with pregabalin that differs from placebo and is of concern?

Response: *The pattern of visual field changes identified with pregabalin are scattered decreases predominately in the periphery. They could generally be detected by decreases in peripheral sensitivity.*

b) Could the Division please provide a list of patient numbers that show this pattern?

Response: *Patients of concern include the patients with visual fields identified by your VF experts and all of those who missed 10 or more points on the VF test. There is not agreement of the patients reported as resolved or explained.*

Patient 014_002013 is listed as having glaucoma as an explanation for the field loss, however, the cup to disc ratio is increased only in the left eye, not the right. The cup to disc ratio listed as abnormal is only 0.5 and the IOP is normal.

Patient 030_118008 is listed as having new data with a normal right eye visual field. The visual field presented is not normal and the left eye is definitely worse.

Patient 034_045003 is listed as having a normal follow-up exam. The VF performed at the follow-up was a 30 degree field, not a full field and did not evaluate where the defects were noted earlier.

Patient 105_501002 is listed as showing a return to baseline OS and worse performance in the right eye with a comment of "poor concentration." Based on the times listed on the fields, the concentration was ok 10 minutes later and there is disagreement that the field returned to baseline.

Patient 1005_508005 is listed as a repeat field 12 days later which is normal (not captured in the database). The field presented is not a normal right eye field.

Patient 127_006006 is listed as showing worsening ARMD. This does not preclude a drug effect.

Patient 131_105014 is listed as having a normal visual field, but only the central 30 degrees is normal.

ATTACHMENT 3

| Page(s) Withheld

 Trade Secret / Confidential

 X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 3

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/s/

Lisa Malandro
8/16/04 05:25:12 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-724

NDA

Pfizer Global Research & Development
Attention: Jonathon M. Parker, R.Ph., M.S.
Global Regulatory Leader, Regulatory Affairs
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Mr. Parker:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: LYRICA (pregabalin) Capsules, 20/50/75/100/150/200/225/300 mg

This application has been administratively split by the Agency according to indication. Two applications have been submitted to this Division. The details for these applications are as follows:

Our Reference Number:	NDA 21-724
Indication:	Epilepsy
Review Priority Classification:	Standard (S)
Date of Application:	October 30, 2003
Date of Receipt:	October 31, 2003
PDFUA Goal Date:	August 31, 2004

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications have been filed under section 505(b) of the Act on December 30, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have not identified any additional review issues for the above applications other than those described in the Agency's January 9, 2004 letter sent to you by the Division of Anesthetic, Critical Care, and Addiction Drug Products.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

NDA 21-724

NDA 21-725

Page 2

If you have any questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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

/s/

Russell Katz
1/13/04 01:50:43 PM