



Pfizer Pharmaceuticals Group

January 12, 2004

The Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: *Docket No. 2003N-0502 – Agency Information Collection Activities; Proposed Collection; Comment Request; Study to Measure the Compliance of Prescribers With the Contraindication of the Use of Triptans in Migraine Headache Patients With Vascular Disease.*
Federal Register/Vol. 68, No. 221/November 17, 2003

Dear Sir/Madam:

We are writing in response to the Agency's request for comments on a proposed web-based survey to evaluate triptan prescriber compliance with the contraindication of use in migraine patients with known vascular disease. Although we endorse safe prescribing of these medications, the proposed study to collect data via the internet has a number of inherent limitations that may produce data that do not accurately reflect real-world prescribing practices. Presented in the following paragraphs is a discussion on some of these design limitations, as well as a possible alternative study design and some suggested changes to the questionnaire which the Agency might wish to consider.

Study Design

Although web-based surveys can significantly reduce turnaround time and costs compared with telephone or mail surveys, there are several potential shortcomings with this mode of data collection that may result in selection and/or information bias. Previous comparisons of telephone/mail surveys and web-based surveys indicate there are significant differences in response propensity by several demographic, health and treatment characteristics including education, sex, age, race, socioeconomic status, computer literacy/access to the internet, and patient satisfaction/dissatisfaction with their physician/treatment. Thus, the target audience for this sample will not accurately reflect the population of triptan users.

More importantly, because respondents to an internet survey are self-selected, they are unlikely to be representative of triptan users on the very characteristic that is being studied. Specifically, respondents to such a survey may be more likely to have adverse events with triptans and medical histories that are positive for pre-existing cardiovascular, cerebrovascular, or peripheral vascular disease. In the absence of a true denominator, the

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prevalence of pre-existing vascular disease among triptan users may be dramatically over-estimated. In addition, the accuracy of self-reported vascular disease on the internet is uncertain. Although this limitation might be partially offset by a medical record review in a subset of respondents to confirm the accuracy of self-report, representative sampling of patient records may be restricted by the Health Insurance Portability and Accountability Act regulations. Finally, because of the unrestricted access to the survey, there is the potential for fraudulent entry of information. Given these methodological issues, it may be difficult to draw valid and meaningful conclusions from this type of study.

The Agency may wish to consider an alternative strategy to evaluate the adherence of prescribers to the triptan labeling guidance. For example, information bias or recall bias (e.g. concomitant medications, medical history), can be avoided by using medical claims and pharmacy databases. Pfizer has recently supported two large epidemiological studies to evaluate the association between the use of triptans and the incidence of cardiovascular and cerebrovascular events using the United Healthcare database in the US and the General Practice Research Database (GPRD) in the UK^{1,2}. In both studies, endpoints were validated for a random sample of patients. The results of these validation studies suggest that the cardiovascular status of patients being treated with triptans can be accurately assessed using automated databases.

By utilizing a large managed care database for the proposed study, it would be possible to identify triptan users through pharmacy data, and then, to determine the rate of vascular disease and risk factors by reviewing the linked medical records. Such an approach would provide a more accurate assessment of the cardiovascular status of the patients being treated with triptans.

Finally, regardless of the approach adopted, we also believe it is important to determine *a priori* what proportion of patients with pre-existing cardiovascular, cerebrovascular or peripheral vascular disease would constitute a "signal" in the study protocol and specify what level of "improvement of risk management" (e.g. further study of the problem, a labeling change, educational programs, increased restrictions on prescribing) will be required in response to the observed "signal". This predetermined "signal" should also be the basis for the sample size calculation.

Study Protocol

Although the FDA has not made the study protocol available for public comment thus far, we would like the Agency to consider the following points for inclusion in the final protocol for the proposed study:

- 1) the rationale and power calculations for the proposed sample size of 500 patients;
- 2) the means by which patients will be "solicited" for participation (via mail, email, websites, doctor offices, pharmacies, etc);
- 3) any proposed incentive for patients to participate in the study;
- 4) the method of review of medical records (e.g., the proportion of patients' medical records that will be reviewed, the means to obtain informed consent, strategies to be used to

address constraints on record access due to HIPAA regulations, party(ies) responsible for medical chart review (the patient's physician, officers of the FDA or FDA representatives), medical record abstracting forms, and other ways of verifying medical history when medical record is not available or incomplete).

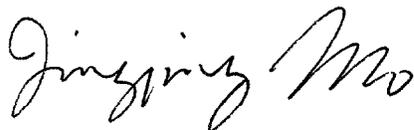
Study Questionnaire

In addition to our suggestion for an alternative study design, we have the following comments on your draft questionnaire:

- 1) As stated in the Federal Register, the proposed study will be conducted in a self-selected sample of triptan users. However, there is no specific question about whether a patient has ever been prescribed a triptan for treatment of his/her migraine headaches.
- 2) Some of the triptans have a variety of formulations, others do not; therefore, only the appropriate route(s) of administration for each triptan should be listed in the questionnaire to avoid invalid data.
- 3) The questions regarding triptan prescribing and medical history are not constructed in a way that the compliance of prescribers can be evaluated appropriately. For example, if a patient was prescribed a triptan ONCE two years ago and had a myocardial infarction 13-months ago, the patient may fill in TWO years to answer the question on 'how long have you been using them?' since there is no other option available, and will select '1-3 years' to answer the question 'how long ago did you had a heart attack'. This would result in a false-positive response.
- 4) It is not clear whether the agency will use the data collected in 'Medications' section to evaluate concurrent or contemporaneous medication use among triptan users. If this is the case, the information collected from the questionnaire is not sufficient to assess whether other medications are taken concurrently or contemporaneously with triptans.

We appreciate your invitation to provide comments on this proposed study and would welcome the opportunity to discuss further refinements in methodology and survey content in the future. Although the internet holds potential for enhancing survey research methodology, it is our opinion that data obtained by such a method cannot be reliably used to understand patterns of prescribing adherence amongst physicians treating migraine.

Sincerely,



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References:

1. Priscilla Velentgas, J. Alexander Cole, Jingping Mo, Carolyn R. Sikes, Alexander M. Walker. Triptan Use Is Not Associated with Increased Risk of Severe Vascular Events in Migraine Patients. 6th Congress of the European Federation of Neurological Societies, Vienna, Austria, October 26-29, 2002. (Manuscript submitted to Headache.)
2. Gillian C. Hall, Martin M. Brown, Jingping Mo, Kenneth D. MacRae. Migraine, Triptan Treatment and the Risk of Cardiovascular Disease, Stroke and Mortality. 6th Congress of the European Federation of Neurological Societies, Vienna, Austria, October 26-29, 2002. (Manuscript accepted by Neurology.)