

January 15, 2004

Dockets Management Branch
Food and Drug Administration (HFA-305)
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Re: 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 [Docket 2003N-0502]

Dear Sir or Madam:

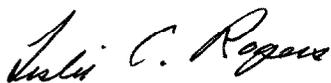
Enclosed please find comments from GlaxoSmithKline in response to FDA's proposal to distribute internet-based questionnaires to Measure the Compliance of Prescribers with the Contraindication of the Use of Triptans in Migraine Headache Patients With Vascular Disease. Public comment regarding the FDA proposal was solicited in its notice in the *Federal Register* on November 17, 2003, Vol. 68, No. 221, pages 64902 to 64903 (Docket No. 2003N-0502).

Although the notice primarily solicits comments on FDA's burden estimates to distribute the questionnaire, FDA also has invited comment on whether the proposed collection of information is:

- Necessary for the proper performance of FDA's functions, including whether the information will have practical utility.
- The validity of the methodology and assumptions used.
- Ways to enhance the quality, utility and clarity of the information to be collected.

Our comments are provided in duplicate. If you have any questions regarding these comments, please contact me at (919) 483-5107.

Sincerely,



Leslie Rogers, MD,
Sr. Director, Neurology Group
US Regulatory Affairs

2003N-0502

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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 [DOCKET NO. 2003N-0502]
NOVEMBER 17, 2003, (FR VOL. 68, NO. 221, 64902- 64903)

On November 17, 2003, the Food and Drug Administration (FDA) issued the above referenced Federal Register Notice. FDA delineates in its notice, plans to conduct a pilot Internet-based study to recruit triptan-user migraine headache patients to determine whether prescribers follow the labeling recommendation to avoid prescribing this class of drugs to patients with pre-existing cardiovascular, cerebrovascular, or peripheral vascular syndromes or with cardiac risk factors. FDA also has specifically invited comment on:

- Whether the proposed collection of information "will have practical utility."
- "The validity of the methodology and assumptions used."
- "Ways to enhance the quality, utility and clarity of the information to be collected."

Described below are comments provided on behalf of GlaxoSmithKline (GSK), the maker of Imitrex® (sumatriptan, sumatriptan succinate) and Amerge® (naratriptan) for the treatment of migraine.

GlaxoSmithKline (GSK) shares a mutual interest with FDA of minimizing the occurrence of avoidable adverse events to patients. However, GSK respectfully suggests that the information collection proposal lacks practical utility because (1) an adequate foundation for investigation has not been established, and (2) even if it had been, the proposed method of investigation is not valid, and is in fact inferior to well-accepted methodological alternatives for conducting exploratory analyses of this kind. Furthermore, even assuming there were reason to move ahead with the proposed information collection, it would be unwise for FDA to proceed without consulting GSK (and other companies, with research, development, and commercial marketing experience with the 7 triptans currently available in the United States) about optimal study design and assessment. In light of these weaknesses, FDA should refrain from conducting the information collection as proposed in the Notice, or at least pause to reconsider its approach and receive further public input.

Absence of adequate foundation

The Agency has not elucidated any data or other information to justify the expenditure of government resources, and the imposition of related information collection burdens,

associated with a study targeting the prescribing of the triptan class of medicines. The entire rationale consists of speculation that "it would be of great use to better understand the prescribing practices as a result of this contraindication [use of triptans in patients with vascular diseases]."

GSK submits this is an insufficient predicate for conducting publicly-funded research that casts a cloud of suspicion over a class of currently marketed drug products that provide great clinical benefit to patients who suffer from migraine headaches. Many marketed drugs -- including treatments for migraine other than the triptan class of medicines -- carry contraindications and/or serious warnings, yet FDA has not explained how or why the triptan class of medicines were targeted for special attention. Guided by evidence-based decision-making, the Agency should not proceed unless it can articulate a data-driven basis for focusing the proposed information collection on the triptan class of medicines to the exclusion of other therapies that could be prescribed outside of label recommendations with potentially dangerous consequences.

Substantive and clinically meaningful contraindications attend the use of multiple other migraine products, including significant cardiovascular contraindications. For instance, Cafergot®, an ergotamine product used for acute treatment and prevention, carries significant contraindications, including significant contraindications for patients with cardiovascular diseases, as do propranolol and Midrin®. To reiterate, no rationale has been offered to explain the sole focus on triptan drugs when data could be richer -- and the speculative risks equally or more serious -- for older drugs with longer use in practice, including ergot alkaloids, Midrin®, and propranolol. It could be argued that the cumulative risk of population exposure to these older drugs is substantially greater than the risk of exposure to the triptan class of medicines which are the newest drugs in the armamentarium of migraine drugs and collectively make up only about 40% of the market volume for acute migraine treatments.

The absence of an adequate foundation is troubling for several reasons. First, it suggests that research costs and information collection burdens might be incurred for no good reason. Second, one can imagine that one regrettable consequence of the sole focus on triptan drugs could be to shift patient use to the older agents that are mistakenly assumed, in light of the study design, to be relatively free of safety risks. Third, the targeting of the triptan class of medicines without data-driven justification is simply unfair. The implication of a current problem, and the tendency to prejudge the outcome, are unmistakable from the Agency's explicit reference to the prospect of "...further action on the sponsor's part to improve risk management ... [to] include further study of the problem, a labeling change, educational programs performed by the sponsor, or increased restrictions on prescribing." In light of the methodological weaknesses of the proposed collection (see next section), and the absence of any specification of what the Agency will consider from this study to be "a signal,"

speculation about such prospects is premature, and reinforces the inequity of selectively targeting triptan drugs without justification.

Methodological weaknesses

The Federal Register describes the proposed activities as a pilot study aimed at providing estimates of the rate of inappropriate prescribing to patients who are current users of the triptan class of medicines. Although FDA acknowledges that the study population obtained through internet-based recruitment may not reflect the population of triptan users at large, it goes on to state:

“...a signal of substantial prescribing to patients with vascular contraindications in this selected population may warrant further action on the sponsor’s part to improve risk management.”

The Agency provides no specific details regarding how FDA intends to implement the questionnaires nor does it describe what it will judge to be a signal that will require action on the part of sponsors. The absence of any prospective and rigorous definition of a "signal," and the sampling basis that FDA has itself identified, are critical flaws. An internet-based, patient directed survey will be inherently biased and provide inaccurate information about the true incidence of use of drugs in the triptan class in patients with underlying vascular disease.

It is well known that spontaneously obtained adverse event data is sensitive to many external factors such as, length of time on the market, media attention (including advertisement by litigation attorneys), regulatory activity, the nature of the disease being treated, and intended use of the medicine. In this regard we believe that reports solicited via an Internet survey will share some of the same shortcomings of selection/reporting bias as spontaneous reports. Since the premise for the questionnaire has now been publicly described, we question how the Agency realistically hopes to ensure a balanced response and quantitatively correlate the number of cases identified with the actual rate of occurrence of inappropriate prescribing among users of the triptan class of medicines.

Although questionnaires offered to patients on the Internet might be useful for pursuing complete assessment of an individual case, they have significant potential to attract patients that disproportionately fit the profile of interest and are not representative of the population of triptan users at large. At best, we would expect such an approach would provide biased information regarding the true rate or strength of “the signal.” Such a survey can only result in equivocal information that in any event would require additional study by more scientifically rigorous methods before it could possibly justify changes in product stewardship. If warranted, the Agency could more systematically and rigorously explore the possibility of inappropriate prescribing via drug utilisation databases it now evaluates, and

via complementary epidemiological research. Resorting to methods with comparatively weak potential to yield meaningful information is not an efficient or appropriate use of resources.

Given the potentially significant impact from decisions FDA could make from its assessment of the information collected, GSK feels it is important to describe the inherent flaws of surveys of this nature in further detail:

- FDA acknowledges that the study population obtained through Internet-based recruitment would most likely not reflect the population of users of triptan drugs at large. We suggest that FDA reconcile this statement with their goal of estimating the rate of inappropriate prescribing.
- It is not made clear how patients will be invited to take part in the survey. We anticipate that an open invitation would result in a significantly biased sample, particularly if the goal of the survey would be mentioned. This bias would not be resolved by the subsequent checking of medical records which is proposed since it will only provide information on the potential case that has been identified.
- Further sources of error inherent in such an approach include coverage, non-response, measurement and sampling error, which are significant in this type of approach.
- Measurement error is introduced due to the survey medium or due to poorly written questions/scales. One drawback of online administration of the proposed survey is that there is no ability to probe responses. This may be more pronounced for a survey where some of the questions may be hard for the respondent to answer, such as concomitant illnesses.
- Sampling error is the error associated with taking a sample of respondents and not a census. In a random sample, each person in the population has a known and equal probability of being selected for inclusion in the sample. It is impractical to conduct a random sample among online respondents. In the online world, most sampling is done using volunteer panels. Online samples tend to be "convenience" samples for which it is extremely risky to make judgements about the size of a particular population, such as an estimate of the incidence of rates of vascular diseases and cardiac risk factors among migraine headache patients using the triptan class of medicines. Thus, we believe that an Internet-based survey is an inappropriate mechanism for assessment of the potential inappropriate prescribing habits of physicians.
- The Federal Register Notice provides no information about the Agency's view of the relative role of data derived from the survey in relation to data from controlled clinical studies, epidemiology studies, and spontaneous medical event reports. However, FDA

describes significant potential material consequences based upon its interpretation of the survey. We are concerned that a small, voluntary survey will provide results that essentially represent testimonial evidence that can only support the hypothesis being evaluated.

- Finally, and perhaps most importantly, we believe that FDA has already worked with sponsors to assure that the potential risks of use of all of these drugs are well characterized and accurately described in labeling. To our knowledge from extensive safety monitoring, there are no new signals from the triptan-class of drugs. Therefore, we question the expenditure of FDA resources to use flawed methodology in order to attempt to quantitate the occurrence of inappropriate prescribing practices for the triptan class of medicines.

Ways to enhance the quality, utility and clarity of the information to be collected

As already described, GSK has grave reservations about the proposed information collection activity, but if FDA decides to proceed, it should certainly pause to consult GSK (and other companies, with research, development, and commercial marketing experience with the triptan class of medicines) about optimal study design and assessment. At a minimum, prior to implementing the proposed collection, FDA should disclose specific details about the proposed collection (*e.g.*, how the purpose of the survey will be explained to patients, a prospective definition of a "signal," *etc.*), and offer a meaningful opportunity for public comment.

Conclusions

GlaxoSmithKline (GSK) agrees that the triptan class of medicines should not be used in patients with pre-existing medical conditions that represent a contraindication for product use. However, we question the Agency's apparent assumption that there is a pattern of inappropriate use that justifies it should single out the triptan class of treatments for migraine for a "pilot" assessment. A suspected risk does not mean that a real risk exists but conducting a study of this nature conveys a perception to patients and prescribers that a problem has been identified. The Agency has not elucidated any data or other information to support expenditure of government resources to complete the proposed survey. The Agency should not proceed unless it can articulate a data-driven basis for its focusing the proposed information collection on the triptan class of medicines to the exclusion of other therapies that could be prescribed outside of label recommendations with potentially dangerous consequences. Based on the information the Agency has provided, we believe that the proposed survey can not reasonably be expected to yield scientifically meaningful data from which evidence-based risk management decisions can be made. We are concerned that flawed methodology and the lack of a description of what FDA might consider to be "a

signal” can only yield an equivocal outcome that could result in the Agency selectively imposing significant new requirements on the triptan class of medicines in the absence of data to justify these measures.

If the Agency has sufficient information to warrant a formal evaluation, we feel that queries of automated databases for an excess frequency of inappropriate prescribing associated with use of the triptan class of medicines versus other potential treatment options, is a more appropriate and scientifically rigorous methodology for FDA to employ. We also believe that before initiating such an evaluation, the FDA should discuss its concerns about possible inappropriate prescribing along with objectives and design of any necessary study with the companies whose products are impacted.