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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

RE: Petition to the Food and Drug Administration to require a black box warning for phosphodiesterase type 5 (PDE5) inhibitor ED drugs (Viagra, Cialis, Levitra) to warn of the potential for irreversible vision loss (HRG Publication #1753).

Dear Sir/Madam,

Pfizer Inc. submits these comments in response to the petition (HRG #1753) filed by Public Citizen's Health Research Group (Public Citizen) and Dr. Howard Pomeranz regarding erectile dysfunction (ED) drugs, including Pfizer's Viagra® (sildenafil citrate), Lilly/ICOS's Cialis® (tadalafil) and Bayer's Levitra® (vardenafil) marketed and distributed by Schering Plough and GlaxoSmithKline, as well as Pfizer's Revatio® (sildenafil citrate) an oral therapy for the treatment of pulmonary arterial hypertension.

In the case of the above petition requesting a black box warning to be added to the labels of the PDE5 inhibitors [Viagra/Revatio; Cialis; Levitra] regarding the risks of drug-induced blindness due to non-arteritic anterior ischemic optic neuropathy (NAION), Pfizer believes the actions requested by the Petitioners to be unwarranted. In response to this petition, Pfizer would like to address four important points:

- 1) there is a large body of data from controlled clinical trials and observational studies that has not been taken into account which shows that the incidence rate of NAION is no different between Viagra patients and those who are not taking Viagra.
- 2) statements have been made and published by a number of ophthalmologists with significant expertise in this area, as well as by the FDA, indicating that there

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is no clear causal association between the use of PDE5 inhibitors, including Viagra, and the development of NAION

- 3) the FDA guidelines for the appropriate use and interpretation of data from their spontaneous adverse event reporting system (AERS) have not been followed, leading to incorrect and misleading conclusions
- 4) the Petitioners have made a number of statements in their petition that are factually inaccurate

Pfizer believes that the FDA has already taken an appropriate stance on this issue, as expressed in the updated product information of the PDE5 inhibitors which indicates the following:

- 1) there have been a small number of cases of NAION reported in patients taking PDE5 inhibitors, the majority of whom had risk factors for developing NAION
- 2) it is impossible to determine what role, if any, PDE5 inhibitors have in the development of NAION as no causal connection has been established
- 3) any patient who experiences a sudden loss of vision should stop taking their PDE5 inhibitor medication and contact their physician

Viagra is the most extensively studied of the three PDE5 inhibitors for over ten years. A number of both clinical and pre-clinical Pfizer-sponsored studies of Viagra have been carried out which have shown no significant negative effects on visual function.¹⁻³ In addition, several independently conducted studies have shown either neutral or positive effects on ocular blood flow.⁴⁻¹⁰ This is particularly relevant to a possible causal association between Viagra (and the other PDE5 inhibitors) and NAION, which is presumed to occur as a result of a decrease in blood flow to the optic nerve.

From the ophthalmologic literature it is known that NAION is the most common acute optic neuropathy in adults over age 50. Two published epidemiologic studies^{11,12} have estimated the annual incidence rate of NAION in the general adult population over age 50 as between 2.3 – 10.3 per 100,000 population. Many of the chronic conditions that are considered to be risk factors for NAION (such as diabetes, hypertension, hyperlipidemia and smoking)¹³ are also well-recognized risk factors for the development of ED, so there is likely to be some overlap among the patients who experience both conditions.

Two of the primary sources of safety data on drugs include clinical trials (which tend to capture more frequent and more carefully conducted patient assessments) and epidemiologic/observational studies (which tend to reflect “real life” use of a treatment in a greater number of patients followed for a longer period of time). Because patients are closely followed in these types of studies, more detailed and reliable information is available about them than that provided through spontaneous adverse event reporting.

An analysis of 103 Viagra clinical studies conducted by Pfizer (which included over 13,400 men studied for over 13,300 patient-years of observation) using the search terms “non-arteritic anterior ischemic optic neuropathy [NAION],” “anterior ischemic optic neuropathy,”

“ischemic optic neuropathy” and “optic neuropathy,” revealed no reports of these conditions among these patients.¹⁴

The Viagra Prescription Event Monitoring (PEM) study (a post-marketing study in the United Kingdom which involved more than 28,000 patients who received a UK National Health Service [NHS] prescription for the drug) is the largest long-term, population-based observational study of Viagra users performed to evaluate its overall safety profile.^{15,16} The study was independently conducted by the Drug Safety Research Unit at the University (DSRU) of Southampton between 1998 and 2001. Two different cohorts comprise the study population; the first cohort of 5,601 patients was observed for a mean of 6 months¹⁶ and the second cohort of 22,473 patients was observed for a mean of 17.5 months.¹⁵ Only one case of NAION, in the second cohort, was reported to the DSRU over the course of the study.¹⁷ This patient was a 61 year old male with a history of cardiovascular disease on several medications who had been taking Viagra for approximately one year when his episode of NAION occurred. As mentioned, given the shared risk factors for both ED and NAION, this case is not unexpected. Based on the approximately 35,500 person-years of observation during Cohorts I and II, the unadjusted incidence of NAION in the PEM study was 2.8 per 100,000 person-years.

The rate of NAION cases seen in the Viagra clinical trials and the post-marketing study mentioned above is well within (and actually at the lower end of) the range reported in the two published epidemiologic studies previously noted (i.e., Johnson and Arnold;¹² Hattenauer¹¹). In the period referred to during which Public Citizen notes the 48 cases of NAION in patients taking Viagra reported to AERS, there have been over 150 million prescriptions filled for Viagra by over 27 million patients worldwide, calculating to approximately 1.9 billion tablets dispensed.¹⁸

Two recent published articles which address the subject of causality of NAION with PDE5 inhibitors are also important to mention here. One by Dr. Fritz Fraunfelder, who founded and maintains The National Registry of Drug-Induced Ocular Side Effects¹⁹ in which the author states “Post marketing surveillance of sildenafil, vardenafil and tadalafil has produced no data to date which confirms a ‘certain’ relationship between ION and ED medications. Present evidence from post marketing surveillance suggests that visual side effects, due to this class of medication, are benign and transitory.” In the second article, Drs. Andrew Lee and Nancy Newman²⁰ state: “Although the case reports to date suggest a possible association between NAION and PDE5 inhibitors, a causal relationship has not been established conclusively.”

In addition to their failure to establish causality, the Petitioner’s request is based on several significant methodological flaws in the Petitioners’ analysis, referring primarily to the inappropriate use of the data from the FDA’s AERS system.

On the FDA website (www.fda.gov), there are several caveats noted regarding the interpretation of adverse event data and the limitations on how such data can be utilized (*emphasis added*):

“There are some important things to keep in mind when reviewing or analyzing AERS data:

- For any given report, there is no certainty that a suspected drug caused the reaction. This is because physicians are encouraged to report suspected reactions; however, the event may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or simply occurred by chance at that time.
- *Accumulated reports cannot be used to calculate incidence (occurrence) rates or to estimate drug risk. Comparisons between drugs cannot be made from these data.*

In Goldman's paper on "The Limitations and Strengths of Spontaneous Report Data,"²¹ the author states "The recognition of adverse drug events... is quite subjective and imprecise. It is well known that placebos and even no treatment can be associated with adverse events. In addition, an underlying background rate almost always exists for any clinical event in a population, regardless of whether exposure to a medicinal product occurred." In addition, he states "The great utility of spontaneous reports lies in hypothesis generation, with the need to explore possible explanations for the adverse event in question.... Spontaneous reporting surveillance programs perform an important function, which is to generate signals of potential problems that warrant further investigation." This particularly applies to systems like AERS which were designed to "cast a wide net" to try to ensure a high degree of sensitivity with less specificity such that, when an adverse event begins to be reported that was not seen in the controlled clinical trials or is being reported at a rate much higher than would be anticipated based on its normal incidence in the population, a "safety signal" is generated. With very few exceptions, such a signal requires further investigation to determine whether it is causally linked to the drug in question or whether it is occurring coincidentally. Such a conclusion can almost never be reached from the spontaneous reports alone.

Further, limitations of post-marketing adverse drug event reporting should be considered when interpreting these data. This includes:

- An accumulation of adverse event reports does not necessarily indicate that a particular adverse event was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.
- Reports are submitted voluntarily, and the magnitude of underreporting (or over reporting, e.g., due to media attention) is unknown.
- Some of the factors that may influence whether an event is reported include: length of time since marketing, *market share of the drug, publicity about a drug, or an adverse event*, seriousness of the reaction, *regulatory actions*, awareness by health professionals and consumers of adverse drug event reporting and litigation
- Clinical information (such as medical history, validation of diagnosis, time from drug intake to onset of event, dose, and use of concomitant drugs) may be missing or incomplete, and follow-up information may not be available. (It is important to note that the AERS system accepts reports from both health care professionals and from the general public and that the latter make it more likely that there may be incomplete

and/or inaccurate information being reported, including second-hand and hearsay data which cannot be corroborated.)

- Many external factors influence whether or not an adverse event is reported, so the spontaneous reporting system yields ***reporting rates not incidence rates***. *As a result, as FDA has stated, it is medically inappropriate to make between-drug comparisons using these rates*

As stated, voluntary reporting systems such as AERS provide reporting rates and not incidence rates. The latter are not possible to calculate from these data since, for any given time interval under consideration, neither the true numerator (ie the total number of occurrences of the event being considered) nor the true denominator (i.e., the total number of people exposed to the drug) are known. It is clear that the Petitioners either did not understand or chose not to follow these guidelines and in their analysis have inappropriately drawn conclusions from the AERS data for which it was never meant to be used.

Of the variables mentioned above that can affect reporting rates, one that may be particularly applicable to Viagra is the publicity that both Viagra in general and the reports of “Viagra and blindness” have received. The Petition (and much of the media coverage on this topic) refers to NAION as leading to “permanent blindness, usually in one eye.” Unfortunately, the word “blindness” may be read by many people to mean a total loss of vision. In the case of NAION, this is an overstatement of the severity of visual loss in many cases, which tends to sensationalize the end-result of this condition. In fact, in the majority of cases, NAION results in either a partial visual field loss with maintenance of good central vision or a decrease in visual acuity (from mild to severe) but with preservation of some vision. The use of such a highly emotional term as “blindness” could mislead and confuse the general public about the actual effect of NAION on vision.

It has also caused some confusion among physicians who have been aware since Viagra’s approval of several extensively studied, well-described mild and transient visual symptoms (e.g., color tinge to vision, increased sensitivity to light or blurred vision) associated with its use in a small percent of patients. It is known that these symptoms are caused by some degree of transient inhibition of phosphodiesterase type 6 (PDE6), the predominant phosphodiesterase in the rod and cone cells of the retina. PDE6 inhibition has not been associated with any serious or long-term visual disturbances and is unrelated to NAION. Yet, because these documented side effects involve the eye, they may be incorrectly lumped together as constituting a serious ophthalmologic problem with Viagra. This results in making any visual adverse effect that patients may experience while taking Viagra that much more likely to be reported. This was confirmed by tracking Pfizer’s own safety reporting database in which there have been “spikes” in the number of NAION reports whenever there has been media coverage of this issue.

Another caveat noted by FDA in using AERS data is that it should not be used to compare reporting rates between or among drugs. Thus, the comparison made in the Petition of reported rates for NAION in patients taking Viagra, Pfizer’s Lipitor® (atorvastatin) and Merck’s Zocor® (simvastatin) is also methodologically incorrect. Aside from the fact that these types of comparisons are inappropriate in general, in this case, in particular, the fact that there have

been no sentinel events of NAION reported with the statins (i.e., in either the scientific literature or the lay press), makes it logical to consider that there is a much greater likelihood that any suspected cases seen in patients taking Viagra will be reported at much higher rates than those occurring in patients on a statin. Patients are also more likely to associate an adverse event with a drug they take sporadically (especially if there may be a temporal association between the last dose of the drug taken and the onset of the event) than one taken daily for a chronic condition such as hypercholesterolemia. These factors would make it more likely that both physicians and patients would think of Viagra as being the cause of the event when, as the FDA states, the actual cause may not be related to the drug at all. Given the number of patients taking Viagra at any given time, the two events (i.e., taking a dose of Viagra and developing an episode of NAION) may be coincidental rather than cause-and-effect.

Finally, there are a number of factual inaccuracies and exclusions in the Petition. These include:

- 1) The Petitioners state that "NAION first came to public attention on May 27, 2005," coincident with the publication of an article published by one of the petitioners, Dr. Howard Pomeranz.²² However, the fact is that, since the initial published case report by Egan and Pomeranz in 2000²³ and the subsequent article by Pomeranz et al in 2002²⁴, both the medical community and the general public have been aware of this. Pfizer has been monitoring the extremely small number of reported instances since these reports first began to appear. All such reported adverse events have been submitted to FDA as part of Pfizer's routine safety reporting procedures.
- 2) Earlier this year, the FDA recommended the addition of the current statements in the Post-Marketing Adverse Event^a and Precaution/Information for Patients^b sections in the USPI. The Petition fails to recognize that at the time these statements were added to the labels of the three PDE5 inhibitors (referred to in the Petition as "professional labels") in July of this year, the FDA also approved revised Patient Package Inserts that include (in consumer friendly language) all relevant NAION-related information to clearly

^a Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (see **PRECAUTIONS/Information for Patients**).

^b Physicians should advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see **POSTMARKETINGEXPERIENCE/ Special Senses**).

communicate what is known about this issue to consumers. It is important to note that the FDA-approved language clearly states that it is not possible to determine whether the events reported are related to PDE5 inhibitors or to other factors. Rather, they state that, in a small number of cases of NAION that have been reported in men taking PDE5 inhibitors, there may have been a temporal association between the two.

- 3) The Petition claims that the current Revatio® (sildenafil citrate) [for the treatment of pulmonary hypertension] label does not mention NAION. Although there have been no cases of NAION reported in Revatio users, the Precaution section of the Revatio label was updated in August of this year to include the NAION statement. (See attached APPENDIX 1)
- 4) The Petitioners request that a separate statement be added to the PDE5 inhibitor labels communicating that men who have had a previous episode of NAION in one eye should not take these drugs. The US PDE5 inhibitor package inserts do, in fact, already include an appropriate guidance.
- 5) The Petitioners also request that a "Dear Doctor" letter be sent to all physicians informing them about the signs and symptoms of NAION. In the case of Viagra, this request has already been fulfilled. A "Dear Health Care Professional" letter was sent out voluntarily by Pfizer in July of this year to all US physicians who had prescribed Viagra at least once in the past year and to all ophthalmologists regardless of whether or not they prescribe Viagra (see attached APPENDIX 2).

The Petitioners refer to the risk factors associated with NAION, breaking them into "disease/lifestyle factors" and those "relating to the anatomy around the optic disk." With respect to the former, the strongest risk factor seen to date is diabetes, but others that have been implied from both studies and anecdotal data include pre-existing hypertension, elevated cholesterol, smoking and/or an arteriosclerotic risk profile. As mentioned, these are also risk factors for developing ED. This makes it likely that there will be an overlap between these two populations. Possibly, men with ED (whether or not they are taking a PDE5 inhibitor) may be at even greater risk for developing NAION than the general adult male population.

The "anatomy" section refers to the observation that almost all published case reports of men who developed NAION while taking a PDE5 inhibitor had a "crowded disk" or "disk-at-risk" (i.e. a "relatively small optic nerve head (disc) with a small to absent cup resulting in a cup-to-disk ratio of 0.1 to 0.2.") in the opposite eye. Although it is a commonly accepted risk factor for NAION, there is still a good deal of confusion around this concept. First, there is a great deal of variability in the disk and cup sizes within the general population such that there is no absolute cut-off between a normal disk and a disk-at-risk. Second, there is no good data on the prevalence of the disk-at-risk among the general population or among men taking PDE5 inhibitors. Third, it is not known how a disk-at-risk predisposes one to developing NAION since the actual pathophysiology is still unclear. Presumably there are many more people who have a disk-at-risk than those who develop NAION, either with or without a PDE5 inhibitor. As Arnold states in his paper "Pathogenesis of NAION,"²⁵ "NAION is presumed to result from circulatory insufficiency within the optic nerve head, but the specific mechanism and location of the vasculopathy remain unproven" and "Optic disk structural features play an unknown role in AION. [The disks] in NAION are most often small in diameter, with small or absent cups,

suggesting to many investigators that "crowding" plays a role in pathogenesis, although exactly how it might do so is unclear." Finally, it is not known how (or even if) taking a PDE5 inhibitor can contribute to the development of NAION in a person with a disk-at-risk. This is particularly perplexing in the case reports involving Viagra in men who had been taking the drug for weeks, months or even years before their episode of NAION occurred. If the drug precipitates an episode of NAION in men with disks-at-risk, one might ask why it would not always occur immediately upon starting to take it?

Based on this, Pfizer agrees with FDA and several experts noted above that, at the present time, there is no solid data to suggest a causal association between NAION and PDE5 inhibitors. Where a temporal association has been suggested, a number of the reported cases occurred well outside the half-life of Viagra (4-5 hours), making the events less likely to be caused by the drug. As stated by Lee and Newman,²⁰

"Although the exact ages for all patients taking sildenafil are unknown, it is assumed that they are older aged and harbor vasculopathic risk factors for both ED and NAION. Thus, a certain number (several hundred to perhaps a few thousand) of spontaneous NAION events would be expected to occur each year in a population of 23 million older aged men using sildenafil. Some of these events (depending on the frequency of use of the drug) would fall by chance alone within six to 36 hours of taking sildenafil. It has been suggested that the symptoms of spontaneous NAION are commonly noted upon awakening, perhaps as a result of nocturnal hypotension. It would, therefore, not be unexpected for the timing of some spontaneous NAION cases to follow the use of sildenafil, a drug frequently used at nighttime. Recollection, selection, and ascertainment bias might also be at play among the retrospective cases reported to date."

Pfizer makes every effort to ensure that the Viagra and Revatio Package Inserts and Patient Package Inserts contain accurate and scientifically supported data to clearly communicate all-important product-related information to both physicians and patients in a timely manner. Pfizer takes the safety of patients very seriously and believes that, based on currently available information, the current labeling appropriately informs doctors and patients about the NAION issue and that any further NAION-related labeling change is unwarranted. In addition, Pfizer believes that ED is an important medical condition, which can have a significant negative impact on the lives of patients and their partners. Pfizer also believes that, not only is a black box warning unnecessary and not supported by data for the reasons already delineated, but that it would also create an unjustified cause for concern which could deter patients who could benefit greatly from Viagra.

Sincerely,



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