


# Petition to the FDA to require a black box warning for erectile dysfunction drugs (VIAGRA, CIALIS, LEVITRA) to warn of the potential for irreversible vision loss (HRG Publication #1753)

October 20, 2005

Andrew Von Eschenbach, M.D., Acting Commissioner
U.S. Food and Drug Administration
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Von Eschenbach:

Public Citizen, representing more than 135,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately add a black box warning regarding the risks of drug-induced blindness for the three phosphodiesterase 5 (PDE5) inhibitors that are prescribed for the treatment of erectile dysfunction [Viagra (sildenafil; Pfizer), Cialis (tadalafil; Lilly), and Levitra (vardenafil; Bayer)]. The label for Revatio, a version of sildenafil indicated for pulmonary arterial hypertension, should also be included in the changes recommended in this petition.

Public Citizen's concern is based, in part, on our findings that 1) Viagra accounts for nineteen percent of the total cases of ischemic optic neuropathy (loss of vision) in the FDA's adverse event database, more than 2-fold higher than that for the next most frequently-cited drug; and that 2) the number of cases of ischemic optic neuropathy per million prescriptions is 18-fold higher for patients taking Viagra compared with patients taking Lipitor, another drug used by people with similar risk factors.

**Additional Requests**

This petition also strongly urges the FDA to require that a "Dear Doctor" letter be sent to all physicians informing them about the signs and symptoms of non-arteritic ischemic optic neuropathy (NAION), an often irreversible loss of vision. Men who have had a previous attack of NAION in one eye should not take these drugs since these men are at increased risk of NAION in the other eye, especially if they have other risk factors such as diabetes and hypertension.

In order to inform patients, FDA should require the mandatory distribution by pharmacists of scientifically accurate information for consumers, written in non-technical language in the form of FDA-approved Medication Guides, with each new and refill prescription for these drugs. The current patient information leaflets (not FDA-approved) are given to patients when a prescription is filled and several patient information leaflets that we have collected do not adequately warn about this serious adverse reaction.

Finally, in order to try and define the causes and prevalence of NAION due to these drugs, FDA should require the manufacturers to establish a registry of all patients diagnosed with NAION and to immediately inform the FDA of new cases.

**Background**

NAION is a pathologic condition triggered by blockage of blood flow to the eye that is sudden but painless in onset and frequently leads to permanent blindness, usually in one eye. The exact causes are unknown, but it often appears upon first awakening and thus has been hypothesized to be precipitated by hypotension occurring during sleep, mainly in people over the age of 50.

NAION first came to public attention on May 27, 2005, when the FDA announced that it was in discussions with Pfizer to update its Viagra label to mention loss of vision. The FDA announcement was apparently triggered by an article published in the March 2005 issue of the Journal of Neuro-Ophthalmology that described seven new cases of NAION apparently linked to the use of Viagra.[1] Although this article produced the first major public focus on the relation of Viagra to this disease, there have been 19 cases in the medical literature implicating the PDE5 inhibitors beginning in 2000 (see ref. 15-24).

After media coverage of the FDA announcement, Senator Charles Grassley became concerned about the lack of any substantive action by FDA and began his own investigation.[2] Grassley's staff interviewed the safety evaluator from the FDA Office of Drug Safety (ODS), who had produced the original analysis of NAION in Viagra users. By monitoring adverse event reports submitted to the FDA, the safety evaluator had concluded, as early as January 2004, that NAION was an important safety issue for Viagra users. Her review had been sufficient to convince the deputy director of the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products that the potential for NAION should be added to the Viagra label. The NAION report was finalized in April 2004 and sent to the Office of New Drugs (OND), the final arbiter of label changes. Nevertheless, it wasn't until July 8, 2005, 13 months after the Office of New Drugs received documents from the safety evaluator, that the FDA finally published safety alerts for patients and healthcare professionals on its web site.[3]

There is now mention of NAION in the Precautions and Adverse Reactions sections of the professional labels for Viagra, Cialis, and Levitra (but no mention anywhere in the label for Revatio). However, the wording is ambiguous and the location of this information is buried: under Information for Patients in the Precautions section (information that usually is not given to patients), there is one untitled paragraph. In the Adverse Reactions section under Post-marketing Experience, one of several paragraphs discusses NAION. In the case of Viagra, NAION is discussed in one of two paragraphs under Adverse Reactions subheaded "Special Senses" which gives no indication as to what is discussed (the other two drugs have paragraphs that are at least titled "Ophthalmologic").

Emphasis in the label is on the word "rarely", downplaying the importance of NAION and is coupled with the caveat that, "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". It is probably true that many factors are involved, but one factor clearly seems to be the drug (see below).

The current label has a paragraph titled "Effects of VIAGRA on Vision" which includes no reference to NAION. This needs to be amended.

**Public Citizen's Analysis**

Public Citizen has been concerned about a number of safety issues with Viagra's use since its approval in 1998 when we asked the FDA to include stronger warnings concerning adverse effects.[4] Public Citizen had, at that time, only looked at the FDA reviews since no postmarketing adverse event data were available. Our concerns relating to the eye were limited to color aberrations, increased sensitivity to light, and blurred vision. However, after the publicity in May 2005 about NAION, we began reading the literature reports and decided to undertake our own analysis using the FDA Adverse Event Reports (AERS) database.

We used the search term "ischemic optic neuropathy" (ION) as recommended by a neuro-ophthalmologist (the term NAION is not present in the AERS database). We searched the entire FDA database from 1/1/98 to 12/31/04 for all reports of ION that showed up for any drug (combining brand and generic names). We found 258 reports in which a drug was listed as the primary suspect for this adverse event.

The three drugs with the highest percentage of reports of ION in the FDA's AERS database were Viagra, interferon, and amiodarone (Table 1). These three drugs (of thousands in the data set) accounted for 42% of all reported ION cases. Viagra had the highest percentage by a factor of more than 2-fold in spite of the fact that during this time period there was no mention of NAION in the label, whereas the labels for both interferon and amiodarone had prominent Warnings and amiodarone had a statement in the Precautions section as well.[5] The fact that Viagra's large numbers of adverse reaction reports occurred without any warnings to the medical profession strongly suggests that Viagra is an important factor in causing ION (*all of these cases accrued before the Viagra-NAION association first came to public attention in May 2005*). All reports are for Viagra, since Revatio had not been approved during the time period we searched.

**Table 1. Ischemic optic neuropathy cases in the AERS database***

| Drug | Number of reports | % of total ION reports |
|---|---|---|
| Viagra | 48 | **19** |
| Interferon | 21 | 8 |
| Amiodarone | 12 | 5 |
| Vioxx | 9 | 3 |
| Lipitor | 10 | 4 |
| Zocor | 2 | 1 |

*1/1/98 to 12/31/04; total number of reports was 258.

**Reports of another well-recognized adverse event**

To put into context and further understand the relevance of the disproportionate percentage of cases of ION in which Viagra was the primary suspect drug, we studied another drug with a well-recognized but rare adverse effect: Lotronex and ischemic colitis (the label for Lotronex now begins with a prominent black box warning). As was the situation for ION, a small number of drugs accounted for a vastly disproportionate percent of reports, showing that unusual adverse events can be identified among the background noise in the AERS system (Table 2). Lotronex and Zelnorm (the first and second in the list) are both drugs approved for irritable bowel syndrome. Although the Zelnorm label lacks Lotronex's black box warning, it does have a paragraph under precautions titled "Ischemic colitis".

**Table 2. Ischemic colitis cases in the AERS database**

| Drug | Number of reports* | % of ischemic colitis reports |
|---|---|---|
| Lotronex | 194 | **23** |
| Zelnorm | 55 | 6 |
| Vioxx | 24 | 3 |
| Remicade | 21 | 2 |
| Celebrex | 12 | 1 |

*1/1/98 to 12/31/04; total number of reports was 852.

**Reporting rate for ION and related terms**

Because reports to the FDA's AERS database may not have used the same preferred terms to describe ION, we used six search terms recommended by neuro-ophthalmologist Dr. Jonathan Trobe at the University of Michigan Medical School: ischemic optic neuropathy (ION), visual field defect, blindness, blindness unilateral, scotoma, or optic nerve infarction. We broke the results into two parts: the reporting rate for ION and that of the other five terms (non-ION). A patient could have ≥1 of these terms.

We tabulated the number of cases of ION for the three PDE5 inhibitors as well as for two statin drugs, since the statins would be given to a similar group of people, i.e., older men more likely to have heart disease and/or diabetes. By dividing the number of cases by the total number of prescriptions filled, we were able to estimate the ION reporting rate for each drug (Table 3). The rate of ION with Viagra was 18 times higher than that with Lipitor, the largest-selling statin drug; Cialis was 25 times higher, but the number of Cialis cases in the database, thus far, is small.

Even though the number of cases of ION is still very small with Cialis, the numbers of prescriptions is very low compared with Viagra (Cialis was approved in November 2003, Levitra in August 2003, and Viagra in March 1998). It is clear, however, looking at the vision-related non-ION terms, that all of these drugs clearly have an adverse effect on the eye. It could be that there were many more cases of ION not reported to the FDA as such, since the numbers of non-ION cases (corrected for the number of prescriptions) are an order of magnitude higher with all three PDE5 inhibitors compared with the two statins.

**Table 3. Ischemic optic neuropathy: Comparison of three erectile dysfunction drugs with two statins, Lipitor and Zocor**

| Drug | ION cases | Number of prescriptions 1/98-12/04 | Cases of ION per 106 prescriptions (X10) | non-ION cases* | non-ION cases* per 106 prescriptions (X10) |
|---|---|---|---|---|---|
| Levitra | 0 | 2.5 x 106 | **0.0** | 6 | **24** |
| Cialis | 2 | 2.7 x 106 | **7.4** | 4 | **15** |
| Viagra | 48 | 89 x 106 | **5.3** | 50 | **6** |
| Lipitor | 10 | 380 x 106 | **0.3** | 32 | **0.8** |

| | | | | | |
|---|---|---|---|---|---|
| Zocor | 2 | 174 x 106 | **0.1** | 8 | **0.5** |

* visual field defect, blindness, blindness unilateral, scotoma, or optic nerve infarction

**PATIENT INFORMATION LEAFLETS**

Patient information leaflets are provided by private companies, not the FDA, and so are not regulated. Some of the current patient information leaflets contain no clear warnings, lump serious and less serious adverse events together, and bury information in large amounts of other material. Readability varies greatly, with small font-sizes and single-spacing being common (see Attachment).

**NAION RISK FACTORS**

Two general types of risk factors for NAION have been studied: disease/lifestyle factors and those relating to the anatomy around the optic disc. Although definitive data are lacking, certain factors appear to predispose individuals to NAION.

Disease/lifestyle

It has been implied, both from studies and anecdotal data that pre-existing hypertension, diabetes, elevated cholesterol, and/or an arteriosclerotic risk profile put patients at risk.[6],[7] However, people taking Lipitor and Zocor fall into a group likely to have these risk factors, yet we find a much lower percentage of cases of ION with Lipitor and Zocor (Table 1).

Diabetes emerged as a risk factor in two studies undertaken before Viagra approval. One case-control study looked at diabetes, hypertension, high cholesterol, coronary artery disease, tobacco use, and body mass index as risk factors for NAION and found that only diabetes was statistically significant.[8] In a larger study (n=326 cases) of people each of whom already had NAION in one eye and was being followed to determine risk factors for NAION in the unaffected eye, 15% developed NAION in the other eye over a 5 year period. Diabetes was the only factor reaching statistical significance (p=0.02)[9] ("Vascular condition" did not quite reach statistical significance with p=0.06.) The potential risk factors of smoking, hypertension, myocardial infarction, cerebrovascular accident, transient ischemic attack, and aspirin use were not statistically significant in this study. In a review of NAION pathogenesis, Arnold stated that, "diabetes is the most consistently identified vasculopathic risk factor".[10]

Nocturnal hypotension may also play an important role: in a study of 544 episodes of NAION, 73% were presented as visual loss upon first awakening.[11]

Anatomy

The anatomic configuration around the optic disc appears to be of great importance in NAION. Many studies have measured the optic cup and optic disc in the unaffected eye in patients with NAION (the optic disc is measured in the non-affected eye because it is obscured by swelling in the affected eye). The optic disc is where the optic nerve enters the back of the eye; the optic cup is where the central retinal artery and vein emerge from within the optic nerve. Measurements from the unaffected eye often showed a relatively small optic nerve head (disc) and a small to absent cup resulting in a cup-to-disc ratio of 0.1 to 0.2[12] (see Figure).

Beck et al. "postulate that the pathogenesis of n-AION [NAION] is multifactorial with the size of optic disc as one important factor", and Bollinger and Lee state that, "Nearly all patients with NAION have a small, crowded optic nerve head ("disk at risk") . . ."[13]

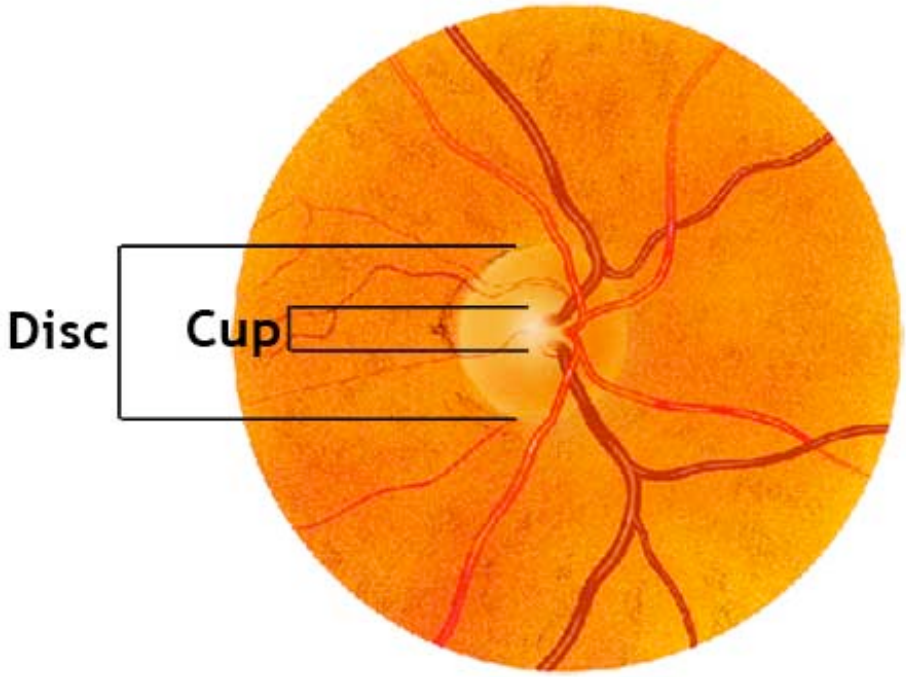


Figure. Back of eye showing optic disc and cup where arteries and veins enter the eye. The disc represents the optic nerve and the cup the region within the optic nerve where the central retinal artery and vein emerge.

**Relation of NAION to PDE5 inhibitors**

Because of so many occurrences of NAION within hours after dosing with PDE5 inhibitors, most authors find it hard not to strongly suspect a cause-and-effect relationship.[14],[15],[16],[17],[18],[19],[20],[21],[22],[23] One case in the literature is especially compelling: a patient suffered somewhat reversible visual field defects within 2 hours of taking each of four doses of Cialis with permanent loss of vision shortly after the fifth dose.[24]

Although the manufacturers deny any causal effect, Cunningham and Smith state that, "The temporal relationship between the doses of sildenafil citrate [Viagra] and the onset of visual loss make it difficult to accept the notion that these were unrelated coincidental events."[25]

Now that sildenafil is also available under the brand name Revatio as long-term therapy for pulmonary arterial hypertension (PAH) with dosing of 20 mg three times a day[26] (on a par with the 25, 50, or 100 mg doses of Viagra), it is even more urgent to determine whether a link exists between these drugs and the development of NAION. Revatio (sildenafil) for PAH is used as long-term daily therapy compared to the sporadic use of Viagra (sildenafil) when indicated for erectile dysfunction. Patient populations are similar.

**Recommendations**

1) FDA should immediately require a black box warning for NAION for the entire PDE5 inhibitor drug class (Viagra, Cialis, Levitra, and Revatio) since the current labeling is inadequate. Although the FDA's safety evaluator recommended NAION be added to both the Precautions and Warnings sections of the Viagra label,[27] at present, there are only two inconspicuous paragraphs (one in Information for Patients under *Precautions* and one in Post-marketing Experience under *Adverse Reactions*) for Viagra, Cialis, and Levitra. These sections have neither titles nor bolding to call attention to this serious adverse event; instead, everything imaginable has been done to detract from its relevance and prominence. The Revatio label has no information at all.

Our model black box warning for NAION—for doctors and patients---would be:

> There have been a significant number of patients taking PDE5 inhibitors (Viagra, Cialis, and Levitra) who have developed non-arteritic anterior ischemic optic neuropathy (NAION), a sudden loss of vision, usually in one eye, that can lead to permanent blindness. Patients should be told to report to their physicians any loss of vision, particularly that occurring upon waking up, not to take any more doses of drug, and to have an immediate eye exam. All physicians are encouraged to question patients appearing with NAION as to their use of these drugs and provide information on its symptoms. Patients who have experienced NAION in one eye are likely at increased risk for a second event, especially if they have other risk factors such as diabetes and hypertension and should not take these drugs.

2) In order to insure that patients receive the needed information, FDA needs to write a Medication Guide for consumers.

3) Because there is still much debate as to the causes, incidence, and risk factors for NAION, we recommend that the FDA have manufacturers establish a registry of patients taking PDE5 inhibitors who develop NAION. This will help clarify the nature of the relationship between drug use and NAION.

4) The manufacturers should immediately send a letter to all Health Care Professionals with all the new information. Health Care Professionals should be encouraged to report to the FDA all cases of adverse events related to the eye.

**ENVIRONMENTAL IMPACT STATEMENT**

Nothing requested in this petition will have an impact on the environment.

**CERTIFICATION**

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

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Peter Lurie, M.D.
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Howard D. Pomeranz, M.D.*

*Howard D. Pomeranz, MD, PhD is a neuro-ophthalmologist who recently joined the Department of Ophthalmology at North Shore Long Island Jewish Health System in Great Neck, NY. He is a Clinical Associate Professor of Ophthalmology. Prior to this, he was an Associate Professor in the Department of Ophthalmology at the University of Minnesota Medical School. He has co-authored several of the published reports about the association between sildenafil and ischemic optic neuropathy.

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[1] Pomeranz HD and Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (Viagra): a report of seven new cases. J Neuro-Ophthalmology 2005;25:9-13.

[2]Grassley C. Letter to FDA. June 24, 2005. Available at http://www.fdaweb.com/source/GrassleytoCrawford62405.doc Accessed 10/15/2005.

[3] FDA Alert on Viagra. July 2005. http://www.fda.gov/cder/consumerinfo/viagra/viagra.htm Accessed 10/15/05.

[4]Letter to FDA from Public Citizen. August 20, 1998. Available at http://www.citizen.org/publications/release.cfm?ID=6649 Accessed 10/15/05.

Petition to FDA from Public Citizen. July 1, 1998. Available at http://www.citizen.org/publications/release.cfm?ID=6644 Accessed 10/15/05.

[5] Amiodarone. *Physicians' Desk Reference*. 59th Ed. Montvale, NJ.: Thomson PDR, 2005. 3256.

Interferon. *Physicians' Desk Reference*. 59th Ed. Montvale, NJ.: Thomson PDR, 2005. 2906.

[6] Pomeranz HD, Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (viagra): a report of seven new cases. J Neuro-Ophthalmol 2005;25:9-13.

[7] Heyreh SS, Joos KM, Podhajsky PA et al. Systemic diseases associated with nonarteitic anterior ischemic optic neuropathy. Am J Ophthalmology 1994;118:766-780.

[8] Jacobson DM, Vierkant RA, Belongia EA. Nonarteritic anterior ischemic optic neuropathy. A case-control study of potential risk factors. Arch Ophthalmology 1999;115:1403-7.

[9] Newman NJ, Scherer R, Langenberg P, et al. The fellow eye in NAION: report from the ischemic optic neuropathy decompression trial follow-up study. Am. J Ophthalmol

2002;134:317-328.

[10] Arnold AC Pathogenesis of nonarteritic anterior ischemic optic neuropathy. J Neuro-Ophthalmol 2003;23:157-163.

[11] Hayreh SS, Podhajsky PA, and Zimmerman B. Nonarteritic anterior ischemic optic neuropathy: time of onset of visual loss. American J of Ophthalmology 1997;124:641-647.

[12] Beck RW, Servais GE, and Hayreh SS. Anterior ischemic optic neuropathy IX. Cup-to-disc ratio and its role in pathogenesis. Ophthalmology 1987;94:1503-1508.

[13] Bollinger K, Lee MS. Recurrent visual field defect and ischemic optic neuropathy associated with tadalafil rechallenge. Arch Ophthalmol 2005;123:400-401.

[14] Dheer S, Rekhi GS Rekhi, Merlyn S. Sildenafil associated anterior ischsaemic optic neuropathy. JAPI 2002;50:265.

[15] Egan R, Pomeranz H. Sildenafil (Viagra) associated anterior ischemic optic neuropathy. Arch Ophthalmol 2000;118:291-292.

[16] Cunningham AV and Smith KH. Anterior ischemic optic neuropathy associated with viagra. J Neuro-Ophthalmol 2001;21:22-25.

[17] Boshier A, Pambakian N., Shakir SAW. A case of nonarteritic ischemic optic neuropathy (NAION) in a male patient taking sildenafil. Int. J Clinical Pharmacol and Therapeutics 2002;40:422-423.

[18] Pomeranz HD, Smith KH, Hart WM and Egan RA. Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. Ophthalmology 2002;109:584-587.

[19] Pomeranz HD, Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (viagra): a report of seven new cases. J Neuro-Ophthalmol 2005;25:9-13.

[20] Bollinger K, Lee MS. Recurrent visual field defect and ischemic optic neuropathy associated with tadalafil rechallenge. Arch Ophthalmol 2005;123:400-401.

[21] Peter NM, Singh MV, Fox PD. Tadalafil-associated anterior ischaemic optic neuropathy. Eye 2005;19:715-717.

[22] Escaravage GK, Wright JD, Givre SJ. Tadalafil associated with anterior ischemic optic neuropathy. Arch Ophthalmol;123:399-400.

[23] Gruhn N, Fledelius HC. Unilateral optic neuropathy associated with sildenafil intake. Acta Ophthalmologica Scand. 2005;83:131-132.

[24] Egan RA, Fraunfelder FW. Viagra and anterior ischemic optic neuropathy. Arch Ophthalmol 2005;123:709-710.

[25] Cunningham AV and Smith KH. Anterior ischemic optic neuropathy associated with viagra. 2001;21:22-25.

[26] Revatio (sildenafil) Professional Product Labeling at www.revatio.com/ Accessed 9/22/05.

[27] http://www.fdaweb.com/source/GrassleytoCrawford62405.doc

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