FDA Alert for Healthcare Professionals

Sildenafil (marketed as Viagra)

The NAION issue has been addressed in product labeling, please see Drugs@FDA. For current information about this drug, see www.fda.gov/cder/consumer/viagra/default.htm

FDA ALERT [07/2005]: FDA has approved new labeling for Viagra, Levitra, and Cialis regarding postmarketing reports of vision loss related to NAION (non-arteritic anterior ischemic optic neuropathy). Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Given the small number of events, the large number of users of PDE-5 inhibitors and the fact that this event occurs in a similar population to those who do not take these medicines, it is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or other factors. We cannot currently draw a conclusion of cause and effect. FDA will continue to evaluate the issue.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of Viagra, please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm

Recommendations

Physicians should:

- advise patients to stop use of all PDE-5 inhibitors 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, which can result in permanent loss of vision.
- 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 PDE-5 inhibitors.

Data Summary

As of May 18, 2005, a total of 43 cases of ischemic optic neuropathy (ION) among patients using the marketed PDE-5 inhibitors (sildenafil, tadalafil, vardenafil) have been reported to the FDA's Adverse Event Reporting System. Since approval, 38 cases have been identified in association with sildenafil, 4 cases have been identified in association with tadalafil and one case has been identified in association with vardenafil. Most of these cases (25/43) appear to be the non-arteritic anterior ischemic optic neuropathy (NAION) subtype. Thirty-six of the 43 cases reported accompanying visual loss, and 26 of these 36 cases reported the visual loss as continuing or permanent. Most of the patients in these cases reported vascular risk factors for NAION that overlap with vascular risk factors for erectile dysfunction (such as age over 50, low

cup to disc ratio, hypertension, diabetes, smoking, etc), making direct attribution to PDE-5 inhibitors not possible. However, the clinical attributes of some of the cases (e.g., a temporal relationship in 19 sildenafil cases, 4 tadalafil cases, and the one vardenafil case, and the report of recurrent ocular symptoms that might reflect NAION in five sildenafil cases and one tadalafil case), raise concern in regard to the role of PDE-5 inhibitors.

The 38 cases reported in association with sildenafil use are summarized below:

Table 1: Demographic characteristics of 38 cases of ischemic optic neuropathy reported in association with sildenafil

Age	Mean 60.3 years, Median 60 years (range, 42 to 74 years) (Age unknown in 5 cases)
Gender	Male 37 cases; Unknown 1 case
Time to Onset†	≤ 6 hrs – 7 cases; ≤ 12 hrs – 10 cases; ≤ 24 hrs – 1 case; ≤ 36 hrs – 1 case; Unclear/Not Reported – 19 cases
Dose	25mg - 1 case; 50mg - 12 cases; 100mg - 6 cases; "50-100mg" - 3 cases; 200mg - 1 case; Unknown/Not reported - 15 cases
Recurrent ocular symptoms	5 cases
Source of Report:	US 30 cases; Foreign 8 cases
Report Year	1998 - 2 cases; 1999 - 2 cases; 2000 - 5 cases; 2001 - 7 cases; 2002 - 6 cases; 2003 - 3 cases; 2004 - 5 cases; 2005 - 8 cases
Outcome	Hospitalized - 2 cases; Hospitalized & disabled - 1 case; Disabled - 22 cases: Required intervention - 6 cases (No outcome reported in 7 cases)

† time to onset after last sildenafil administration

The majority of sildenafil cases (21/38) appear to be cases of NAION. It was not possible to definitively subtype (e.g. arteritic vs nonarteritic, posterior vs anterior) the remaining 17 ischemic optic neuropathy cases because of limited information that was provided. Thirty-one of the 38 cases reported accompanying vision loss that was continuing or permanent in 22 cases. Visual loss was not documented in the remaining 7 cases. In nineteen of the 38 cases, diminished vision or vision loss was reported from "immediately" after to 36 hours after sildenafil administration. Twenty-nine of the 38 cases reported one or more of the following risk factors for developing NAION: history of hypertension in 14 cases, history of hyperlipidemia in 12 cases, a low cup to disk ratio or "crowded disc" in 11 cases, history of diabetes in 6 cases, history

of coronary artery disease in 3 cases, history of smoking in 3 cases, history of hypotension in 1 case, and previous history of ION in 1 case.