

**BWC POSITION REGARDING CARDIOVASCULAR CONDITIONS
ALLEGED TO BE CAUSED BY USE OF VIOXX®
(November 18, 2004)**

I. PURPOSE

The purpose of this document is to review the available information regarding the relationship between the use of Vioxx® by injured workers and the risk of developing cardiovascular disease and to provide guidance to BWC staff and Disability Evaluator Panel physicians in addressing issues of claim allowance for cardiovascular diagnoses alleged to be secondary to the use of Vioxx®.

II. INFORMATION ABOUT VIOXX®

On September 30, 2004 Merck & Co., Inc. announced a voluntary worldwide withdrawal of Vioxx® (rofecoxib), a COX-2 selective, non-steroidal anti-inflammatory drug.¹ This medication was approved by the United States Food & Drug Administration in 1999 for the treatment of pain associated with osteoarthritis, management of acute pain in adults, and for the treatment of menstrual symptoms.²

This decision was based on data collected from a prospective randomized, placebo-controlled clinical trial known as APPROVe (Adenomatous Polyp Prevention on Vioxx). This study was designed to evaluate the efficacy of Vioxx® 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. This trial began in 2000 and had enrolled 2600 patients to receive either Vioxx or placebo. According to Merck representatives, the study showed an increased relative risk for confirmed cardiovascular events such as heart attack and stroke beginning after 18 months of treatment in patients receiving Vioxx compared to those receiving placebo.

While the exact results of the study have not been released to date, preliminary analyses were presented at the Annual Scientific Meeting of the American College of Rheumatology on October 18, 2004. The information released states “there were 25 confirmed CV (CardioVascular) events in 3315 patient years on placebo (0.75 events per 100 pt-years) and 45 confirmed CV events in 3041 patient years on rofecoxib (1.48 events per 100 pt-yrs). The relative risk of a confirmed CV event was 1.96 (95% CI 1.20, 3.19; p=0.007). The relative risk for an APTC endpoint (Antiplatelet Trialists’ Collaboration) was 2.25 (95% CI 1.24, 4.08; p=0.008). The results primarily reflect imbalances in myocardial infarctions and ischemic cerebrovascular events. Although these results reflect an increased relative risk over the entire study period, the results for the first 18 months did not show an increased relative risk of confirmed CV events. The increased relative risk was observed beginning after 18 months of treatment. No difference in overall mortality was observed between treatment groups.”³

III. INFORMATION ABOUT CARDIOVASCULAR DISEASE

From the press releases by Merck and the FDA, it appears the cardiovascular disease observed in the study was an increased relative risk of thrombotic events manifest as stroke and myocardial infarction. According to the Centers for Disease Control, heart disease and stroke are the principal components of cardiovascular disease and are the first and third leading causes of death for both men and women in the United States representing 40% of all deaths or over 930,000 deaths annually. Over 64 million Americans live with cardiovascular disease and the projected cost due to heart disease and stroke is projected to be \$368 billion in 2004 including health care expenditures, death, and disability.⁴

Cardiovascular diseases for the most part are the result of atherosclerosis. Risk factors for the development of atherosclerosis that are not modifiable include age, male gender, and genetic or hereditary factors. Modifiable risk factors that can be improved by life-style changes include smoking, obesity, and physical inactivity. Risk factors that may be modified by life-style change or medication include lipid disorders, hypertension, and diabetes mellitus.⁵

Therefore, cardiovascular conditions are common conditions particularly in older individuals that have significant known risk factors that contribute to the development of the condition including aging and other medical conditions.

IV. LITERATURE REVIEW PERTAINING TO CARDIOVASCULAR EVENTS AND USE OF COX-2 MEDICATION

One of the earliest studies noting a potential increased incidence of cardiovascular events was the VIGOR (Vioxx Gastrointestinal Outcomes Research) Study. This study was designed to compare the incidence of confirmed upper gastrointestinal events in 8076 patients with rheumatoid arthritis who were randomly assigned to receive either Vioxx® (rofecoxib) 50 mg daily or naproxen 500 mg twice per day. The mortality rate was 0.5 percent in the Vioxx® group and 0.4 percent in the naproxen group. Rate of death due to cardiovascular causes was 0.2 percent in both groups. Ischemic cerebrovascular events occurred in 0.2 percent of patients in each group. Myocardial infarctions were reported in 0.1 percent of patients in the naproxen group and 0.4 percent of patients in the Vioxx® group providing a relative risk of 0.2. Four percent of study participants reportedly met the criteria of the FDA for the use of aspirin for secondary cardiovascular prophylaxis (presence of a history of myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, angioplasty, or coronary bypass) but were not taking low-dose aspirin therapy. This group of patients accounted for 38 percent of the patients in the study who had myocardial infarctions. Eliminating this group of patients, the myocardial infarction rate was 0.2 percent in the Vioxx® group and 0.1 percent in the naproxen group. It was theorized that naproxen had a coronary protective effect by inhibiting the production of thromboxane and inhibiting platelet aggregation.⁶

Mukherjee et. al.,⁷ reviewed all randomized, double-blind trials of COX-2 inhibitors published in English language from January 1998 to February 2001 to assess whether COX-2 inhibitors were associated with a protective or hazardous effect on the risk of

cardiovascular events. Four studies were identified with the two major studies being the VIGOR study with 8076 participants and the Celecoxib Longterm Arthritis Safety Study (CLASS) with 8059 participants. According to this report, cardiovascular events in the VIGOR study were referred for adjudication of the vascular event that occurred in the participants. This represented 65 of 4047 patients in the Vioxx® treatment group and 33 of 4029 from the naproxen group. Of these, 45 patients (46 events) in the Vioxx® group and 20 patients (20 events) in the naproxen group were determined to have had a serious thrombotic cardiovascular adverse event. The relative risk of developing a cardiovascular event in the Vioxx® treatment group was 2.38. When subgrouping the treatment groups in regard to aspirin indicated patients, the relative risk of developing serious cardiovascular events among aspirin-indicated patients between the Vioxx® group and the naproxen group was 4.89. In comparing the relative risk for the groups where aspirin was not indicated, the relative risk was 1.89. The CLASS study compared the use of celecoxib 400 mg twice per day versus ibuprofen 800 mg three times per day versus diclofenac 75 mg twice per day. Aspirin use was permitted during this study. Cardiovascular event data supplied to FDA reportedly showed no difference in cardiovascular events in comparison of the three medication regimens. Two other studies were reported which compared the use of Vioxx® 12.5 mg per day to nabumetone 1000 mg per day or to placebo. The sample size was 1042 and 978 participants in these studies. Participants were allowed to use low dose aspirin for cardiac protection. These two studies failed to show any increased incidence of cardiovascular events but the sample size was small, the dose of Vioxx® was less than other studies, and participants were allowed to use low-dose aspirin.

Another study by Ray et. al. found that patients using Vioxx® in doses higher than 25 mg per day were 1.70 times more likely than non-users to have a serious cardiac event, but users of Vioxx® at 25 mg or less per day had no evidence of increased risk of cardiac event. Cardiac events or serious coronary artery disease was defined as hospital admission for acute myocardial infarction or death from coronary heart disease. The study population consisted of individuals in the Tennessee Medicaid Program (TennCare) from January 1, 1999 to June 30, 2001.⁸

An article by FitzGerald reports that the APPROVe study showed an increase in the incidence of serious thromboembolic adverse events in the patients receiving Vioxx® 25 mg by a factor of 3.9 and the incidence rates between the two groups diverged progressively after a year or more of treatment.⁹

The articles by FitzGerald and Mukherjee offer an explanation for the observed increased incidence of cardiovascular events observed in individuals using Vioxx®. According to these articles, the COX-2 inhibitors, including Vioxx®, are a subclass of nonsteroidal anti-inflammatory drugs designed to inhibit cyclooxygenase-2 (COX-2) enzymes. The COX-2 enzymes produce prostaglandin E₂ (which mediates inflammation and pain). Recently it has been learned that prostaglandin I₂ is also inhibited by COX-2 inhibitors. Prostaglandin I₂ is the predominant cyclooxygenase product in the endothelium whose actions involve inhibiting platelet aggregation, preventing proliferation of vascular smooth muscle cells, and causing vasodilatation. Cyclooxygenase-1 (COX-1) enzymes are the source of prostaglandin production in the gastric epithelium which is protective of the gastric mucosa. In platelets, COX-1 produces thromboxane A₂ which causes platelet aggregation, vasoconstriction, and vascular proliferation. Therefore, by inhibiting prostaglandin I₂ and not affecting

COX-1 enzymes and the production of thromboxane A₂, COX-2 inhibitors increase the risk of thrombotic events. This risk is reduced with the use of aspirin and other NSAIDs which inhibit both thromboxane A₂ and prostaglandin I₂. This would explain the relative lower risk of cardiovascular event in studies where patients also were using low-dose aspirin or other NSAIDs such as naproxen. How long the risk is present after cessation of Vioxx® is unknown, but as stated by FitzGerald “Patients in the APPROVe study should continue to be followed. This will allow some estimate of how quickly the developed risk may dissipate. Given the relatively short half-lives of these compounds, such a dissipation may occur rapidly. On the otherhand, if treatment has accelerated atherosclerosis, the offset of risk may be more gradual.”⁹

V. RELEVANT OHIO STATUTE AND CASE LAW

The Ohio Revised Code 4123.01 (C) defines “injury” to include “any injury, whether caused by external accidental means or accidental in character and result, received in the course of, and arising out of the injured employee’s employment”. The same statute specifically states that injury does not include “Injury or disability caused primarily by the natural deterioration of tissue, an organ, or part of the body”.

Ohio Revised Code 4123.01 (F) states “Occupational disease means a disease contracted in the course of employment, which by its causes and the characteristics of its manifestation or the condition of the employment results in a hazard which distinguishes the employment in character from employment generally, and the employment creates a risk of contracting the disease in greater degree and in a different manner from the public in general.”

In considering strength of evidence or threshold for proof, Rule 4123-3-09(C)(3)(e) of the Ohio Administrative Code states “Preponderance of the evidence means greater weight of evidence, taking into consideration all the evidence presented. Burden of proof does not necessarily relate to the number of witnesses or quantity of evidence submitted, but to its quality, such as merit, credibility, and weight. The obligation of the claimant is to make proof to the degree of probability. A mere possibility is conjectural, speculative and does not meet the required standard.”

Several court cases have upheld the legal standards for medical evidence requiring the standard of proof as “probable” or “more likely than not” for medical opinions. These include:

Fox v. Indus. Comm. (1955), 162 Ohio St. 569: “Competent medical evidence is required to prove causation in a workers’ compensation case. Medical evidence must show that the injury was or probably was a direct and proximate cause of the harm or disability.”

Drakulich v. Indus. Comm. (1940), 137 Ohio St. 82: “The testimony of the medical witnesses must show a probability, and not a mere possibility that there was a causal relationship.”

McKees v. Cincinnati Street Co. (1949), 152 Ohio St. 269: “Proof of possibility is not sufficient to establish a fact, probability is necessary.”

Stacey v. Carnegie-Illinois (1951), 156 Ohio St. 3d 205: “Expert medical opinion evidence must establish a probable and not a mere possibility of such causal connection.”

Mcwhorter v. Excello Corp. (1990), Allen County: “When medical evidence is necessary to establish proximate cause, such evidence must be based on probabilities. The medical evidence offered in this case is conjecture, a mere possibility, and, as such, it is insufficient to establish proximate cause.”
Therefore, using words “could be considered related” or “possibly considered related” is not sufficient.

One of the key elements that will need to be addressed in any request for allowance of a cardiovascular condition as a result of treatment with Vioxx® will be to establish “causality” or to link the use of the medication (exposure) with the development of the cardiovascular condition or at least acceleration of or (aggravation) of the condition. The following rules and court decisions are important to the issue of causality:

Ohio Administrative Code 4123-3-09 states the “the burden of proof is upon the claimant (applicant for workers' compensation benefits) to establish each essential element of the claim by preponderance of the evidence.”

Aiken v. Indus. Comm. (1944), 143 Ohio St. 113 “The proximate cause of an event is that which in a natural and continuous sequence, unbroken by any new, independent cause, produces that event and without which that event would not have occurred.”

Fox v. Indus. Comm. (1955), 162 Ohio St. 569 “It is necessary for the claimant to show by a preponderance of the evidence that a direct and proximate causal relationship exists between his injury and his harm or disability”.

The issue of “aggravation of pre-existing” is addressed in Ohio Supreme Court ruling in *Schell v. Globe Trucking, Inc., (1990)* that “a work-related aggravation of a pre-existing condition does not have to be of any particular magnitude in order to entitle the claimant to a determination of benefits under the State Insurance Fund. Accordingly, we conclude that the trial court did not err when it determined that the aggravation in this case did not have to be “substantial” in order to entitle Shell to participate in the fund.”

In deriving an opinion of causality or causal relationship, the physician should rely on historical information available to him/her including that obtained from the applicant and medical records, findings from the physician's examination, the results of any studies performed, and the physician's knowledge and expertise. Key factors to consider in deriving an opinion include:

- Whether the medical records or examination support the diagnosis;
- Whether the alleged mechanism of injury, exposure, or work activity more likely than not would result in the injury or illness;

- The time of onset (direct and proximate cause) or chronological sequence;
- The duration of exposure or activity and whether sufficient to cause disease;
- Typical non-occupational disease manifestations and causes;
- Common or known conditions which commonly occur as a result of a given exposure;
- Other contributing factors such as non occupational activities or medical conditions; and
- The response when the applicant is away from the alleged exposure or inciting activity.

VI. DISCUSSION

From the available information regarding Vioxx® to date, increased relative risk of cardiovascular events attributed to the medication was observed in those individuals who have been prescribed the medications for at least 18 months and usually in a dose of at least 25 mg per day. While the exact statistics from the APPROVe study have not been released, preliminary information indicates the risk of a cardiovascular event is small but was twice as great for patients receiving the drug compared to patients receiving a placebo. It is known the study had only 2600 participants and they were of the age when cardiovascular events and diseases are more commonly observed in the general population. Based on the information available to date, it is unknown how many study participants had known pre-existing cardiovascular disease, had other risk factors for cardiovascular disease, or whether prophylactic aspirin was used when indicated.

Other studies and a preliminary report on the APPROVe study indicates the relative risk for cardiac event in users of Vioxx® to be somewhere between two and 3.9 times the risk of study participants who were not using Vioxx®. The incidence rates for cardiovascular events in most of these studies were less than 2% in those individuals using Vioxx®. For example, in the VIGOR study, there were 65 events in 4047 patients receiving Vioxx® or 1.6%. Therefore, the number of observed cardiovascular events in all these studies is relatively low.

From known medical literature, several risk factors including the major risk factors listed above are associated with cardiovascular diseases. These conditions are usually diagnosed later in life and the process is a progressive type of disorder. Given the high prevalence of cardiovascular diseases in western societies and that cardiovascular diseases are usually manifest at an older age as a cardiovascular event such as myocardial infarction or stroke, such events frequently can be considered to be part of the process of aging and natural deterioration.

Whether it can be stated that Vioxx® is a significant enough factor to contribute to an aggravation of a cardiovascular condition in a specific claim is unknown. It can be stated that the medical literature to date does not provide sufficient evidence of continuation of the risk (aggravation of disease process) once Vioxx® is discontinued. This would be difficult to prove particularly given the high prevalence of the conditions and the known risk factors for development and progression of the cardiovascular diseases. In most cases, the most that can be reasonably stated is that use of the medication (Vioxx®) possibly or theoretically contributed to the condition,

but it can not be stated the use of Vioxx® probably contributed or was the most important factor given the low incidence rate of Vioxx®-associated cardiovascular events in the studies to date. Also, once an individual is no longer taking the medication, it is presumed that the effect of the medication is reduced to baseline shortly thereafter as the enzymes resume normal functioning. Therefore, the risk of any cardiovascular event attributed to Vioxx® would be reasonably expected to diminish within a few weeks of stopping the medication (Clearance of medication and resumption of enzyme activity).

In assessing claims requesting an allowance of cardiovascular disease attributed to use of Vioxx®, physician reviewers and examiners should consider the medical records available at the time of initial diagnosis of the condition. These documents may include emergency room reports, hospitalization records, diagnostic studies such as stress tests, thallium scans, and cardiac catheterization reports, and physician office records describing the symptoms, findings, and usually risk factors. To date, the reported increased relative risk of cardiovascular disease was noted primarily in those patients who had received Vioxx® for a considerable period of time (18 months) and at a dose of 25 mg or greater. The magnitude of the risk in comparison to other risk factors is not available. Another key factor to consider is the date of occurrence of any cardiovascular event and the date of stopping the use of Vioxx®.

In summary, it can be stated that cardiovascular diseases are common in the general population and have several major risk factors that contribute to the development of the conditions. Without specific contribution by the workplace or unless covered by separate statute, most cardiovascular conditions appear to be not work related and can be considered natural deterioration of the cardiovascular system. Vioxx® has been associated with increased risk in a relatively small number of patients presumably due to increased risk of thrombosis due to its effect on enzymes that affect the clotting system. The amount of risk that can be attributed to Vioxx® versus other risk factors is unknown. While it is conceivable and possible that Vioxx® could accelerate or aggravate pre-existing cardiovascular disease, there is no data to date to quantify this or to help establish a probable (more likely than not) likelihood particularly given the progressive natural history of these conditions which includes life threatening and life-ending episodes.

VII. RECOMMENDATIONS

Based on the available information to date and the reported mechanism of action leading to any cardiovascular events when using Vioxx®, the following recommendations are made:

- a. An opinion that a cardiovascular event is related to the use of Vioxx® must take into consideration all other risk factors commonly associated with cardiovascular disease. At the least, an opinion that a cardiovascular event is causally related to the use of Vioxx® should be supported by:
 - i. The cardiovascular event must be a *newly* diagnosed thrombotic cardiovascular event such as myocardial infarction, unstable angina, cardiac thrombus, ischemic stroke, transient ischemic attacks (TIAs), cardiac arrest, or sudden or unexplained death that appears to be related to or result of an acute cardiovascular event. Adequate medical records

- supporting the diagnosis which in most cases should include Emergency Room and Hospital Records pertaining to the specific event;
- ii. The individual must have taken Vioxx® at least 18 months;
 - iii. The dose of Vioxx® used is 25mg or more per day;
 - iv. The event happened while using Vioxx® or within 30 days of discontinuing the use of Vioxx® for at least 18 months;
 - v. Vioxx® must have been prescribed for treatment of a work-related condition and paid by BWC;
 - vi. The cardiac event more likely was not related to or the result of other risk factors for cardiovascular disease.

It is important that reviewing or examining physicians consider all risk factors commonly associated with cardiovascular disease that may be present and discuss the relevance of those factors to the specifics of the case.

- b. For claim allowance requests for cardiovascular events that occurred after November 1, 2004 (30 days post date of manufacturer withdrawal of medication), the request should most likely be denied since the apparent mechanism of action of Vioxx® causing the event should have resolved. It is important that reviewing or examining physicians consider all risk factors commonly associated with cardiovascular disease that may be present and discuss the relevance of those factors to the specifics of the case.
- c. For claim allowance requesting aggravation of pre-existing cardiovascular event or disease, there is no evidence that the use of Vioxx® causes aggravations without a thrombotic event during the period of use. It is important that reviewing or examining physicians consider all risk factors commonly associated with cardiovascular disease that may be present and discuss the relevance of those factors to the specifics of the case.

This position paper will be updated as more information regarding Vioxx® becomes available.

¹ “Merck Announces Voluntary Worldwide Withdrawal of VIOXX®” @ http://www.merck.com/newsroom/press_releases/product/2004_0930.html verified September 30, 2004.

² “FDA Public Health Advisory: Safety of Vioxx” @ http://www.fda.gov/cder/drug/infopage/vioxx/PHA_vioxx.htm verified September 30, 2004.

³ “VIOXX Cardiovascular Safety Data from the APPROVe Study” presented at American College of Rheumatology Annual Scientific Meeting, San Antonio, October 18, 2004.

⁴ “Preventing Heart Disease and Stroke: Addressing the Nation’s Leading Killers” @ http://www.cdc.gov/nccdphp/aag/aag_cvd.htm verified September 30, 2004.

⁵ Libby, P.: “Prevention and Treatment of Atherosclerosis” in Harrison’s Principles of Internal Medicine-15th Edition, McGraw-Hill Publishers, 2001. pp.1382-1386.

⁶ Bombardier C, et. al.: “Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis” The New England Journal of Medicine 343:1520-1528, 2000.

⁷ Mukherjee D, Nissen SE, and Topol, EJ: “Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors” Journal of the American Medical Association 286:954-959, 2001.

⁸ Ray WA, Stein CM, et. al.: “COX-2 Selective Non-Steroidal Anti-Inflammatory Drugs and Risk of Serious Coronary Heart Disease” The Lancet 360:1071-1073-2002.

⁹ FitzGerald GA: “Coxibs and Cardiovascular Disease” The New England Journal of Medicine 351:1709-1711, 2004.