2005

Food and Drug Administration and its Regulatory Practices on Vioxx: Three Perspectives

Anna Soraya Magtoto

Food and Drug Administration and its regulatory practices on Vioxx:

Three perspectives

By:
Anna Soraya Magtoto

Table of Contents

My Mission

My mission is to gather perspectives from three different categories of individuals who are involved in the area of drug research, drug marketing and application and as the recipient of the drug thought to be safe enough for public consumption. This research will talk on the evolution of drug law in the United States, which includes the Food and Drug administration, the Center for Drug evaluation and Research, a brief look at International drug regulation with a return to a local act called the Prescription Drug User Fee Act. I will be focusing on VIOXX (Rofecoxib) as the drug, which has brought to the public's attention the Food and Drug administration.

Evolution of Drug Law in the United States

I remember watching a wild west movie of long ago where there was a scene involving a cart, a salesman in a cowboy hat and bottles of what were known in the days as elixirs that were suppose to cure any type of ailment (i.e. gout, arthritis, headaches, etc.). These so called elixirs were only mere water, ethyl alcohol and whatever else the salesman thought to mix in a vat and sell them for a profit. Needless to say that people ended up feeling ill than being cured.

These incidents of poisoning prompted in 1906, the Food and Drug Act, but it was not until the late 1937 when the Elixir of Sulfanilamide tragedy killed 107 individuals which caused considerable public outcry, that the act was fully codified as what is known today as the Food Drug and Cosmetic Act of 1938. This act contains the following new provisions:

- Requiring new drugs to be shown safe before marketing-starting a new system of drug regulation.
- Eliminating the Sherley Amendment requirement to prove intent to defraud in drug misbranding.
- Extending control to cosmetics and therapeutic devices.
- Providing that safe tolerances be set for unavoidable poisonous substances.
- Authorizing standards of identity, quality and fill-of-container for foods.
- Authorizing factory inspections.

- Adding the remedy of court injunctions to the previous penalties of seizures and prosecutions.

1962 was the year of the Thalidomide tragedy. Thalidomide was developed in Europe as a sedative hypnotic which had been noted as not having major noted side effects for individuals who have taken the drug until it was discovered that 8000 children from 46 countries were born with debilitating birth defects. This tragedy resulted in a series of activities worldwide that emphasized safety related testing and fetal development and gestation testing associated with the development of new medicinal products. Thalidomide was not fully experimented on prior to its release for use by the public; the limited data on toxicology testing was not present as well as animal modeling to ensure that its compound was safe for the human race.

Spared by this tragedy was the US. It wasn't until an individual from the Food and Drug Administration, Frances Kelsey, saw some indications in the preliminary toxicology testing that cautioned her to prevent administration and approval of the drug in this country. She is solely credited with preventing a whole generation of children in the US from suffering severe birth defects associated with Thalidomide. The Thalidomide situation provides an excellent example of FDA's purposes and tasks. The agency exists to protect the public.

International Good Clinical Practices

As companies conduct global clinical trials, adhering to good clinical practices is more challenging but equally important as in US-based trials. It is important to remember the purpose of good clinical practices regardless of clinical trial location.

GCP are the ethical, scientific and quality standards for designing, conducting, recording and reporting trials that involve human subjects to ensure the protection of the rights, safety and well being of study subjects; Clinical study data are credible; Improvement of the overall quality of clinical research; Mutual acceptance of data.

The General GCP Principles include:

- Adhere to ethical principles of the Declaration of Helsinki, applicable regulatory requirements and the protocol.
- Roles/responsibilities established for investigators, sponsors/monitors and IRBs/IECs.
- Trials conducted by qualified individuals
- Voluntary patient consent is obtained
- Obtain IRB/IEC approval prior to initiation
- Availability of relevant non-clinical and clinical information
- Recording/retention of all trial information to allow reporting and verification
- Protect confidentiality of subjects
- Implementation of systems and procedures to assure quality of the trial data generated

International Conference on Harmonisation (ICH)

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

The objective of such harmonization is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

ICH Guidelines

The ICH Topics are divided into four major categories and ICH Topic Codes are assigned according to these categories.

Q

"Quality" Topics, i.e., those relating to chemical and pharmaceutical Quality Assurance. Examples: Q1 Stability Testing, Q3 Impurity Testing

S

"Safety" Topics, i.e., those relating to in vitro and in vivo pre-clinical studies. Examples: S1 Carcinogenicity Testing, S2 Genotoxicity Testing

E

"Efficacy" Topics, i.e., those relating to clinical studies in human subject. Examples: E4 Dose Response Studies, Carcinogenicity Testing, E6 Good Clinical Practices. (Note Clinical Safety Data Management is also classified as an "Efficacy" topic - E2)

M

"Multidisciplinary" Topics, i.e., cross-cutting Topics which do not fit uniquely into one of the above categories.

- M1: Medical Terminology (MedDRA)
- M2: Electronic Standards for Transmission of Regulatory Information (ESTRI)
- M3: Timing of Pre-clinical Studies in Relation to Clinical Trials
- M4: The Common Technical Document (CTD)
- M5: Data Elements and Standards for Drug Dictionaries

Food and Drug Administration

Mission Statement

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

What the FDA regulates

FDA is the federal agency responsible for ensuring that foods are safe, wholesome and sanitary; human and veterinary drugs, biological products, and medical devices are safe and effective; cosmetics are safe; and electronic products that emit radiation are safe. FDA also ensures that these products are honestly, accurately and informatively represented to the public. Some of the agency's specific responsibilities include:

Biologics

- product and manufacturing establishment licensing
- safety of the nation's blood supply
- research to establish product standards and develop improved testing methods

Cosmetics

- safety
- labeling

Drugs

- product approvals
- OTC and prescription drug labeling
- drug manufacturing standards

Foods

- labeling
- safety of all food products (except meat and poultry)
- bottled water

Medical Devices

- premarket approval of new devices
- manufacturing and performance standards
- tracking reports of device malfunctioning and serious adverse reactions

Radiation-Emitting Electronic Products

- radiation safety performance standards for microwave ovens, television receivers, diagnostic

- x-ray equipment, cabinet x-ray systems (such as baggage x-rays at airports), laser products,
- ultrasonic therapy equipment, mercury vapor lamps, and sunlamps
- accrediting and inspecting mammography facilities

Veterinary Products

- livestock feeds
- pet foods
- veterinary drugs and devices

What it does not regulate

- Advertising
- Alcohol
- Consumer Products
- Drugs of Abuse
- Health Insurance
- Meat and Poultry
- Pesticides
- Restaurants and Grocery Stores
- Water

FDA Responsibilities

First and foremost, the FDA's task is to **protect** the public. Therefore, the agency looks at its roles, in each of the aspects of the development and evaluation process, as doing just that. FDA is the check and balance for conducting research to ensure that products have adequate safety and efficacy to be released. They do so by evaluation the scientific rigor, the conduct, the details and whether the research has been carried out according to the investigative and development plan.

This role even extends to the early release of medical products for life-threatening diseases or for diseases that have no other alternative treatments. An expedited approval program is in place to make sure that patients have the best possible opportunity to get medication and other treatments that did not previously exist for their conditions. However, following the release of that product to the public, FDA will look very carefully at the ongoing data collected for that product. Currently, expedited programs for diseases such as AIDS, Alzheimer's, Cancer and other rare diseases are frequently seen.

Center for Drug Evaluation and Research (CDER)

The Center for Drug Evaluation and Research (CDER), which assures that safe and effective drugs are available to the American people, has gone through a functional and organizational metamorphosis since it began as a one-man operation to assess significant drug problems in the marketplace on the eve of the 1906 Pure Food and Drugs Act. In part, this change reflects the evolution of drug law and the

chemotherapeutic revolution over the 20th century--and the concomitant changes in responsibilities of the Food and Drug Administration. But the change also reflects external and internal decisions on how best to provide safe and effective drugs to patients. Every branch of government, as well as other interests affected by FDA's policies, has had a role in the way this agency regulates drugs.

Drug Development and Review Definitions

- Accelerated Development/Review
- Advisory Committee Meeting
- Animal Testing
- Applicant (Drug Sponsor)
- Biopharmaceutical Review
- Chemistry Review
- Clinical Hold Decision
- Clinical Studies
- Institutional Review Board
- Investigational New Drug Application
- Labeling Review
- Medical Review
- Meetings with Sponsors
- Microbiology Review
- New Drug Application
- New Drug Application Actions
- Parallel Track
- Pharmacology/Toxicology Review
- Phase I Clinical Studies
- Phase 2 Clinical Studies
- Phase 3 Clinical Studies
- Pre-Clinical Research
- Review by CDER
- Refuse to File Letter
- Site Inspection
- Statistical Review
- Synthesis and Purification
- Treatment Investigational New Drug

The New Drug Development Process

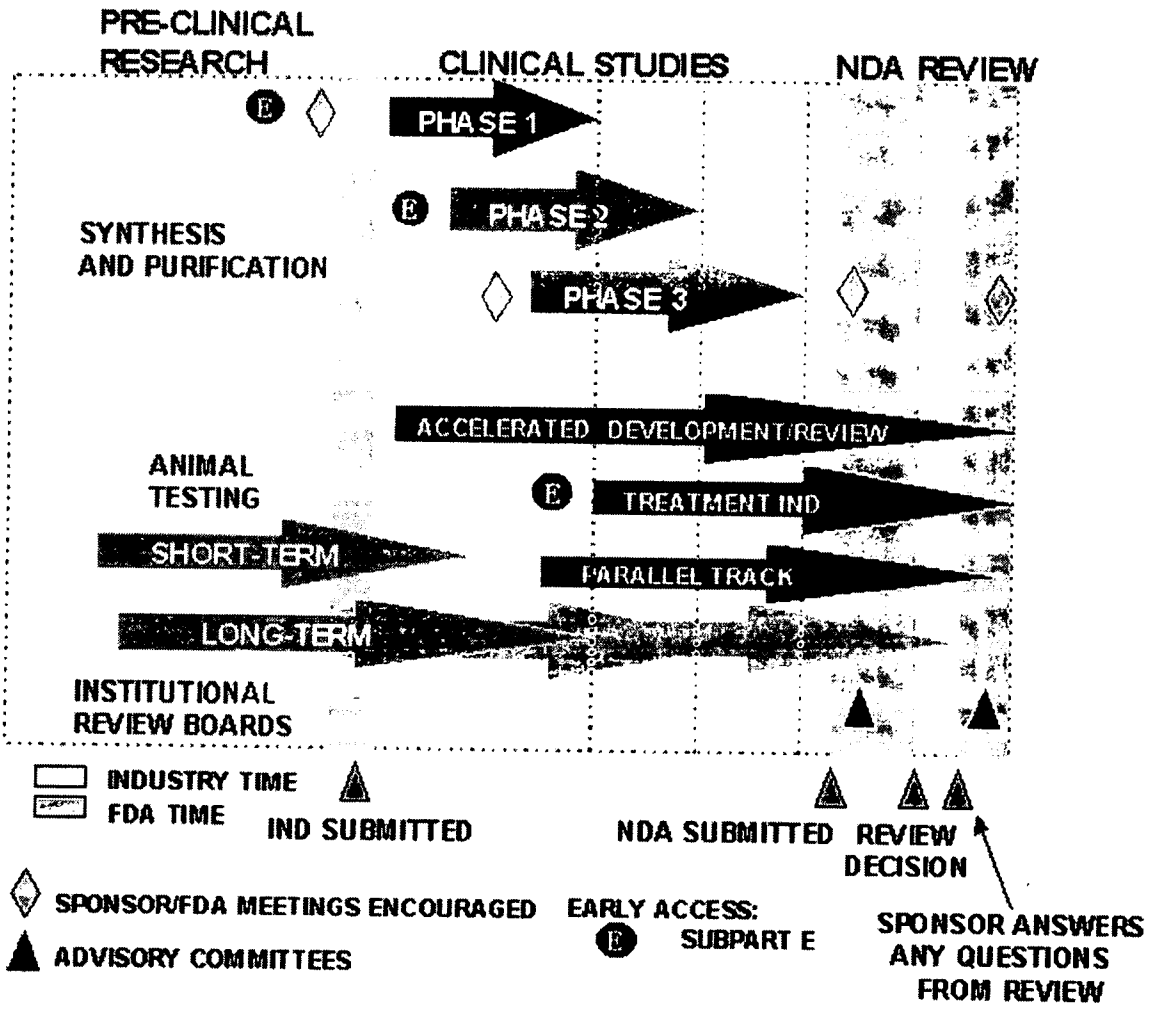


***Chart provided by the CDER handbook on the new drug development process

FDA Timeline

1906 Food and Drug Act: This was the first drug law prohibiting interstate commerce of misbranded and adulterated foods and drugs. The law required that drugs meet certain standards of efficacy and purity. According to the law, before a drug could be taken off the market FDA had to demonstrate that a drug's labeling was false and fraudulent.

1938 Federal Food, Drug and Cosmetic Act: a bill was introduced into the Senate in 1933 to completely revise the 1906 drug law. This act included a revision requiring a manufacturer to prove the safety of a drug before it could be marketed.

1951 Humphrey-Duram Act: Until this law, there was no requirement that any drug sold by prescription only. The amendment defined prescription drugs as those unsafe for self-medication and which should therefore be used only under a doctor's supervision. The law effectively separated drugs into two groups: (1) Those used safely in self-medication and sold without prescription (OTC). (2) Those requiring medical supervision and a prescription (Rx).

1962 Kefauver-Harris Amendment: Congress passed these amendments to tighten control over drugs. Before marketing a drug, firms now had to prove not only safety, but also effectiveness for the product's intended use. The requirement was applied retroactively in 1938, when the FDA Act was passed. With the implementation of the amendments, firms were required to send adverse reaction reports to FDA and drug advertising in medical journals it was required to provide complete information to doctors.

1992 **Prescription Drug User Fee Act**

Prescription Drug User Fee Act (PDUFA)

In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA). This was reauthorized by the Food and Drug Modernization Act of 1997 and again by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. PDUFA authorized FDA to collect fees from companies that produce certain human drug and biological products. Any time a company wants the FDA to approve a new drug or biologic prior to marketing; it must submit an application along with a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed. Previously, taxpayers alone paid for product reviews through budgets provided by Congress. In the new program, industry provides the funding in exchange for FDA agreement to meet drug-review performance goals, which emphasize timeliness.

What comes along with timeliness is the fastrack on decisions to approve breakthrough drugs in six months or less and on all other drugs in 12 months or less. The resources provided by the PDUFA bring important products to patients more quickly and without sacrificing appropriate medical review. The Agency's obligation is to make decisions on time. But a decision does not mean the drug is approved and available to patients. It is also relevant to look at the number of products approved vs. the time of approval. Prior to PDUFA in 1996 the Agency approved twice as many drugs in half the time. All drugs approved by the FDA are important, but none are as meaningful in bringing hope to patients as **new molecular entities** (NMEs). These are new medicines that have never been marketed before in the US. The number of NMEs approved each year is regarded

as a real indication of meaningful medical progress. In 1996 the FDA approved 53 NMEs, referring back to the average annual total of NMEs during the passage of the Kefauver-Harris amendments in 1962, the average annual total of NMEs in that decade in 13.7. In the 1970s the figure went up to 17.3. In the 80s, the average was 21.7 NMEs and in the first half of the 90s, the average was 25.6 NMEs. The latter half of the 1990s showed the figure of 53 NME approvals in 1996, which is more than double what was noted during the first half of the 1990s. (See Figure 1 and Figure 2)

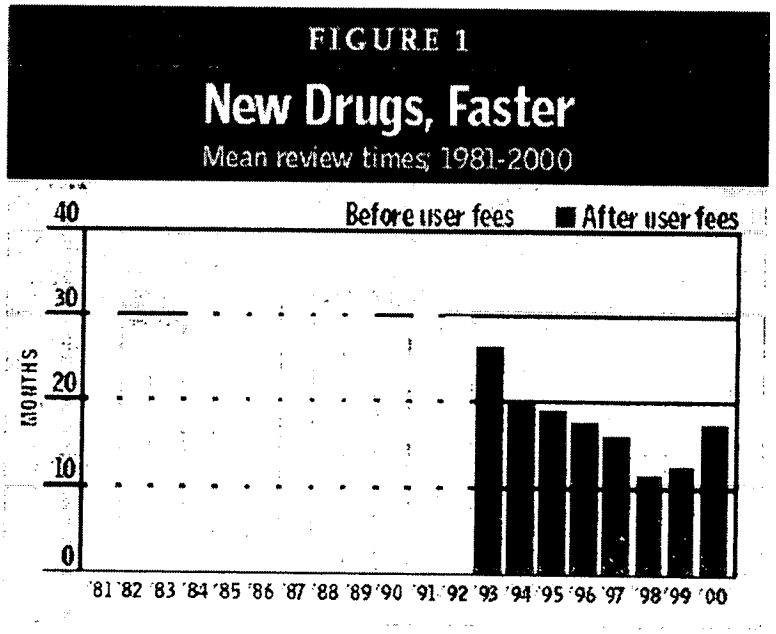
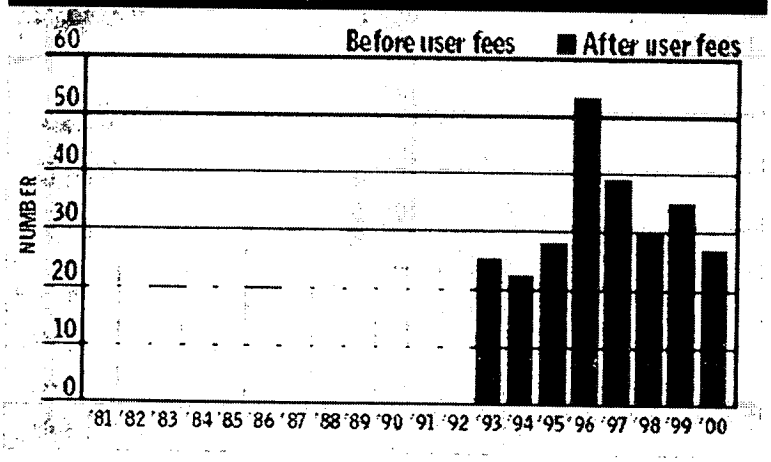


FIGURE 2

More New Drugs

NME approvals; 1981-2000



Scrutiny of the PDUFA is loud and clear. Experts and scholars say there is a conflict of interest. A pharmaceutical company paying the FDA an application fee to expedite the process as to whether a new molecular entity (NME) or compound as it is commonly known can be introduced to the public for preventing or curing an ailment or life threatening illness. According to the testimony of Michael A. Friedman MD, lead commissioner of the FDA, these fees have extraordinarily changed the lives of many Americans as it the fees have helped hire the much needed personnel to review the efficacy of a drug and get them out to market much sooner than is expected. Are we in for another Thalidomide tragedy?

"Respiratory infections, headache, dizziness, diarrhea, nausea, vomiting, upset stomach, heartburn, stomach pain, swelling of the legs and/or feet, High blood pressure, back pain, tiredness and Urinary tract infection"

According to the patient product information for rofecoxib (VIOXX), these are the more common, but less serious side effects reported.

What is Rofecoxib (VIOXX)?

VIOXX is a prescription medicine called a COX-2 selective inhibitor, nonsteroidal anti-inflammatory drug (NSAID).

What is a COX-2 selective inhibitor?

It is a form of NSAID that directly targets COX-2, an enzyme responsible for inflammation and pain. Selectivity for *COX-2* can halve the risk of peptic ulceration, and is the main feature of rofecoxib and other members of this drug class. Cox-2-selectivity does not seem to affect other side-effects of NSAIDs (most notably an increased risk of renal failure), and some results have aroused the suspicion that there might be an increase in the risk for heart attack, thrombosis and stroke by a relative increase in thromboxane.

COX-2 Candidates

- **Celecoxib (CELEBREX)**
- **Valdecoxib (BEXTRA)**
- **Rofecoxib (VIOXX)**

Rofecoxib was taken off the market by Merck in 2004 because of these concerns. Valdecoxib was taken off the market on April 7, 2005 by the request of the Food and Drug Administration.

Risks and side effects

This cardiovascular risk of COX-2 specific inhibitors is not surprising since prostaglandins are involved in regulation of blood pressure by the kidneys. Therefore, cardiovascular effects of NSAIDs prescribed for arthritis pain and inflammation need to be considered when choosing the appropriate medication for each patient.

Medical Opinion

Vioxx or Celebrex?

A French study of osteoarthritis patients over 65 years of age determined that, compared to Celebrex (200 mg once daily), patients taking Vioxx (25 mg once daily) suffered a two-fold increase in clinically significant edema and 60% more frequent increases in systolic blood pressure greater than 20 mmHg, as early as the second week of treatment. This has significant implications, since it has been estimated that every 2 mmHg increase in blood pressure raises the risk of stroke by two thirds and the risk of myocardial infarction by one third, suggesting that Celebrex may be a better choice for hypertensive patients or those at risk for edema. In addition, COX-2 inhibitors lack some of the platelet inhibiting properties of aspirin and other nonspecific NSAIDs and may, directly or indirectly, lead to increased risk of thrombosis, particularly in high risk patients where low dose aspirin therapy is warranted. On the other hand, this property makes them a

better choice for perisurgical pain management, where inhibition of blood clotting would be problematic.

There are other differences between Celebrex and Vioxx that influence prescribing practices. Patients with known sensitivity to sulfa drugs are likely to be sensitive to Celebrex as well, due to similarity in structure. Vioxx has a more rapid onset and is approved for acute pain as well as osteoarthritis, while Celebrex is approved for rheumatoid arthritis as well as osteoarthritis.

Clinical Trials

The VIGOR study

The VIGOR study was designed to evaluate the comparative GI safety of VIOXX 50 mg once daily (twice the highest dose) recommended for chronic use in OA and RA versus naproxen 500 mg twice daily (common therapeutic dose). The general safety and tolerability of VIOXX 50 mg once daily versus naproxen 500 mg twice daily was also studied and it was found that it a showed a higher incidence of adjudicated serious cardiovascular thrombotic events in patients treated with VIOXX 50 mg once daily as compared to patients treated with naproxen 500 mg twice daily. This finding was largely due to a difference in the incidence of myocardial infarction between the groups. Adjudicated serious cardiovascular events included: sudden death, myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack and peripheral venous and arterial thromboses.

The Approve Trial

The Adematous Polyp Prevention on VIOXX (APPROVe) Study was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (3 years) of treatment with rofecoxib (VIOXX), a selective COX-2-inhibiting NSAID, on the recurrence of neoplastic colon polyps in patients with a history of colorectal adenoma. The trial enrolled 2600 patients with no history of any cardiovascular disease and compared rofecoxib 25 mg to placebo.

Of the patients assigned to rofecoxib, 3.5% suffered a myocardial infarction (MI) or stroke, as opposed to 1.9% of the patients assigned to placebo ($P < 0.001$). The difference with regard to thrombotic cardiovascular events became discernable after 18 months and then continued.

The Vioxx Approval Process

FDA originally approved Vioxx in May 1999. The original safety database included approximately 5000 patients on Vioxx and did not show an increased risk of heart attack or stroke. A later study, VIGOR (VIOXX GI Outcomes Research), was primarily designed to look at the effects of Vioxx on side effects such as stomach ulcers and bleeding and was submitted to the FDA in June 2000. The study showed that patients taking Vioxx had fewer stomach ulcers and bleeding than patients taking naproxen, another NSAID, however, the study also showed a greater number of heart attacks in patients taking Vioxx. The VIGOR study was discussed at a February 2001 Arthritis Advisory Committee and the new safety information from this study was added to the labeling for Vioxx in April 2002. Merck then began to conduct longer-term trials to obtain more data on the risk for heart attack and stroke with chronic use of Vioxx.

Vioxx received a six-month priority review because the drug potentially provided a significant therapeutic advantage over existing approved drugs due to fewer gastrointestinal side effects, including bleeding. According to the FDA a product undergoing a priority review is held to the same rigorous standards for safety, efficacy, and quality that FDA expects from all drugs submitted for approval.

First Perspective: Clinical Investigators

1. Based on your past experience conducting clinical trials, describe your relationship with pharmaceutical companies in terms of their monitoring and regulatory functions.

-The response from the clinical investigators is that they have had a good relationship with the pharmaceutical companies in regards to clinical research.

2. Have you experience being audited by the FDA?

- One out of the three investigators has been audited by the FDA.

3. If so, would you say that their safety and monitoring practices to be thorough?

- In response to the first three questions raised to Clinical Investigators, 2 out of 3 physicians have pointed out that the safety and monitoring practices of the FDA relies too much on the data being presented to them by the Pharmaceutical companies.

4. Since 1997, congress has implemented a fee for sponsor companies to include in their IND application as it helps speed along the process. Critics have stated that it is a conflict of interest. Do you agree or disagree with this 'fee'?

- One investigator was not aware of the fee. Another investigator finds it a conflict of interest.

5. Does the 'fee' really help get new drugs to the market faster?

- Two out of the three revealed that the fee for service is not regulated properly to identify and categorize which drugs should be expedited and which drugs should adhere to longer safety data prior to its release to the public.

Second Perspective: Physicians

1. A physician from the New Jersey Institute of Technology commented that after the drug has become available to the public, it is the physicians who must report events brought to their attention by the patients.

-All three physicians pointed out during the interview that there is no suitable reporting system in place to report health events related to patients taking a newly released drug to the public.

2. Have the Pharmaceutical companies and the FDA implemented a suitable reporting system for physicians such s yourself to report events involving a particular drug which a patient of yours has taken?

- All three of the physicians interviewed noted that they know of no such reporting system.

3. Have patients you've prescribed Vioxx and Celebrex in the past ever complained of cardiac-related symptoms?

- All three physicians noted no report of cardiac-related symptoms.

4. What is your opinion on why Celebrex is still on the market and the rest of the Cox-2 inhibitors are gone?

- All three physicians say "good question". But one believes that because he was one of the clinical investigators on a long-term Celebrex trial there has been noted evidence

that the drug is safe for long-term use on low doses. As opposed to what the Vioxx trials have revealed.

Third Perspective: Patient

1. Were you prescribed Vioxx for an ailment?

- *Both patients were prescribed Vioxx for an ailment.*

2. What was the ailment?

- *Both patients noted the ailment as Arthritis related.*

3. Given the fact that Merck withdrew Vioxx after a colorectal Cancer trial revealed that at high doses it has doubled the risk of heart problems among patients. Shouldn't the FDA have taken the lead in advising patient consumers when data showed these events?

- *Both patients felt that the FDA should have advised consumers earlier when data was presented.*

4. Now that the FDA is allowing Vioxx to return with heavy labeling of the risks involved with taking the medication and Merck is not willing to produce the product. In your opinion, should Vioxx return?

- *Two patients have benefited from their use of Vioxx but have each experienced mild to severe cardiovascular related events and were advised to stop its use. They stated that they would be wary of taking Vioxx again now knowing of the risks involved in taking the drug.*

Policy Recommendations

- FDA needs to implement a mandatory delay in approving an NDA for drugs to be used in non-life threatening situations till results of their own department findings have been completed verifying that the drug in question is safe for human use in the long-term setting.
- FDA needs to properly identify which classes of drugs should be considered under the expedited approval process and to delegate that these drugs must only be considered for those patient population who are under life-threatening situations.
- Implement a suitable reporting system for the medical community to utilize in the event an unusual occurrence has been experienced by a patient who has recently taken a drug newly released and/or is within its first five years of release to the public.

Appendix

Declaration of Helsinki
Transcripts of Interviews
- Michael A. Harris, MD
- David Maccini, MD
- Francisco Badar, MD
- Assunta Santos

Vioxx Drug Insert
Vioxx Timeline
Prescription Drug User Fee Act (PDUFA)

Declaration of Helsinki

Policy

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in

accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

---

[1] **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] **Note of clarification on paragraph 30 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

9.10.2004

Transcripts

Transcripts

Interview with Michael A. Harris, MD. Dr. Harris is a Board Certified Medical Oncologist from Mission Viejo, California. He has given consent to this interview and its publishing.

1. Based on your past experience conducting clinical trials, describe your relationship with pharmaceutical companies in terms of their monitoring and regulatory functions.

So far, the pharmaceutical companies have been useful. They do their job and so far their monitoring of the trials I have held have been approved so far.

2. Have you experience being audited by the FDA? Yes

3. If so, would you say that their safety and monitoring practices to be thorough? My experience with them was more on an auditing basis questioning about certain Investigators.

4. Since 1997, congress has implemented a fee for sponsor companies to include in their IND application as it helps speed along the process. Critics have stated that it is a conflict of interest. Do you agree or disagree with this 'fee'?

Disagree

5. Does the 'fee' really help get new drugs to the market faster?

It seems to be as there have been so many new drugs out to market much quicker than before.

As a Physician...

1. A physician from the New Jersey Institute of Technology commented that after the drug has become available to the public, it is the physicians who must report events brought to their attention by the patients.

As a physician, I can only do so much as what the patient would disclose to me. Because I am a specialist in Oncology, more of the ailments that would be brought to me would be that of those related to their cancer. And most of the time the patients are already on several types of medication it would be difficult to pinpoint the culprit of a certain event.

2. Have the Pharmaceutical companies and the FDA implemented a suitable reporting system for physicians such s yourself to report events involving a particular drug which a patient of yours has taken?

Not that I know of.

3. Have patients you've prescribed Vioxx and Celebrex in the past ever complained of cardiac-related symptoms?

No. They would usually end up in the emergency room or they would be referred to their Primary Care Physician.

4. What is your opinion on why Celebrex is still on the market and the rest of the Cox-2 inhibitors are gone? Good Data I guess.

As a patient...

1. Were you prescribed Vioxx for an ailment? Yes

2. What was the ailment?

I have a heel problem of which at this point is becoming arthritic and the pain can at times be an inconvenience.

3. Given the fact that Merck withdrew Vioxx after a colorectal Cancer trial revealed that at high doses it has doubled the risk of heart problems among patients. Shouldn't the FDA have taken the lead in advising patient consumers when data showed these events?

Because the data is presented to the Pharmaceutical company first, the FDA may not have first hand to know that there is something wrong and should be stopped right away

4. Now that the FDA is allowing Vioxx to return with heavy labeling of the risks involved with taking the medication and Merck is not willing to produce the product. In your opinion, should Vioxx return?

It could return, but knowing the risks and being a physician myself, I would recommend taking only the smallest effective dose possible.

Interview with David Maccini, MD. Dr. Maccini is a Board Certified Gastroenterologist located in Spokane, WA. He has given consent to this interview and its publishing.

1.Based on your past experience conducting clinical trials, describe your relationship with pharmaceutical companies in terms of their monitoring and regulatory functions.

My experience has been good with the pharmaceutical companies, I have done several trials involving my specialty of Gastroenterology.

2. Have you experience being audited by the FDA?

No.

3. If so, would you say that their safety and monitoring practices to be thorough?

Not Applicable.

4. Since 1997, congress has implemented a fee for sponsor companies to include in their IND application as it helps speed along the process. Critics have stated that it is a conflict of interest. Do you agree or disagree with this 'fee'?

I did not know there was a fee that the Pharmaceutical companies had to pay.

5. Does the 'fee' really help get new drugs to the market faster?

Not Applicable.

Interview with Francisco Badar, MD. Dr. Badar is a Family Practitioner from Detroit, MI. He has given consent to this interview and its publishing.

1. A physician from the New Jersey Institute of Technology commented that after the drug has become available to the public, it is the physicians who must report events brought to their attention by the patients.

Working at a hospital that sees a certain population in the Detroit area comprising of African-Americans, most of the time they are seen in the emergency room and don't see the same physician every time. We have a difficult time assessing their status especially when they would only reveal or even remember certain medications they are taking. And we don't have the time nor the resources to report events if we ever can pinpoint which drug may be at fault.

2. Have the Pharmaceutical companies and the FDA implemented a suitable reporting system for physicians such s yourself to report events involving a particular drug which a patient of yours has taken? Not that I know of.

3. Have patients you've prescribed Vioxx and Celebrex in the past ever complained of cardiac-related symptoms?

I have only been prescribing Celebrex and it is usually at the lowest dose and so far I have not received any complaints.

4. What is your opinion on why Celebrex is still on the market and the rest of the Cox-2 inhibitors are gone?

Good question. I'm not quite sure.

Interview with Assunta Santos. Ms. Santos was a former Vioxx user from Taiwan. She has given consent to this interview and its publishing.

1. Were you prescribed Vioxx for an ailment? Yes.

2. What was the ailment? I have arthritis in my joints.

3. Given the fact that Merck withdrew Vioxx after a colorectal Cancer trial revealed that at high doses it has doubled the risk of heart problems among patients. Shouldn't the FDA have taken the lead in advising patient consumers when data showed these events? I'm not familiar with the FDA.

4. Now that the FDA is allowing Vioxx to return with heavy labeling of the risks involved with taking the medication and Merck is not willing to produce the product. In your opinion, should Vioxx return?

I really have no opinion, but I do know that because it was the culprit in my experiencing a rise in my blood pressure, my doctor has advised me to no longer take it. I don't think I will take it if it becomes available again.

Vioxx Drug Insert

Patient Information about

VIOXX® (rofecoxib tablets and oral suspension)

VIOXX® (pronounced "VI-ox")

for Osteoarthritis, Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Pain and Migraine Attacks

Generic name: rofecoxib ("ro-fa-COX-ib")

You should read this information before you or your child start taking VIOXX*. Also, read the leaflet each time you refill a prescription, in case any information has changed. This leaflet provides only a summary of certain information about VIOXX. The doctor or pharmacist can give you an additional leaflet that is written for health professionals that contains more complete information. This leaflet does not take the place of talking with your doctor about your condition or treatment. If you have questions about VIOXX ask your doctor or pharmacist.

What is VIOXX?

VIOXX is a prescription medicine called a COX-2 selective, nonsteroidal anti-inflammatory drug (NSAID). (See section "What is VIOXX used for?")

Who should not take VIOXX?

Do not take VIOXX if you or your child:

- have had an allergic reaction such as asthma attacks (wheezing), hives, or swelling of the throat and face to aspirin or other medicines called non-steroidal anti-inflammatory drugs (NSAIDs). There are many NSAID medicines. Ask the doctor or pharmacist for a list of medicines that contain NSAIDs if you are not sure.
- are allergic to rofecoxib, the active ingredient of VIOXX, or to any other ingredients in VIOXX. See the end of this leaflet for a complete list of ingredients in VIOXX.

What are the possible side effects of VIOXX?

Serious but rare and potentially life-threatening side effects that have been reported in patients taking VIOXX include:

- Serious stomach problems, such as stomach and intestinal bleeding, can happen with or without warning symptoms. These problems, if serious, could lead to hospitalization or death. Although this does not happen often, you should watch for the signs and symptoms (for instance, stomach burning, vomiting blood, or if there is blood in the bowel movement or it is black and sticky like tar). Call your doctor right away if you or your child have any of these serious side effects.

- Serious allergic reactions include the symptoms and signs of swelling of the face, lips, tongue; trouble breathing such as chest tightness or shortness of breath; trouble swallowing; hives; wheezing; or shock (loss of blood pressure and consciousness). Get emergency help right away if you get any of these symptoms or signs. Serious skin reactions have also been reported.

- Heart attacks and other serious cardiovascular events, such as blood clots in your body have been reported in patients taking VIOXX.

- Serious kidney problems can happen, including acute (sudden) kidney failure and worsening of chronic kidney failure.

---

*Registered trademark of MERCK & CO., Inc.

- Severe liver problems, including hepatitis, jaundice and liver failure, can occur. Call your doctor if you or your child gets any of these symptoms of liver problems. These include: nausea; itching; pain in the right upper abdomen; yellow skin or eyes; or flu-like symptoms.

Your doctor may do blood tests and check you or your child for problems that may happen during treatment with VIOXX.

More common, but less serious side effects reported with VIOXX have included the following:

- Respiratory infections
- Headache
- Dizziness
- Diarrhea
- Nausea, vomiting and upset stomach
- Heartburn
- Stomach pain
- Swelling of the legs and/or feet
- High blood pressure
- Back pain
- Tiredness
- Urinary tract infection.

In addition, the following side effects have been reported: anxiety, blurred vision, colitis, confusion, constipation, decreased levels of sodium in the blood, depression, fluid in the lungs, hair loss, hallucinations, increased levels of potassium in the blood, insomnia, low blood cell counts, menstrual disorder, palpitations, pancreatitis, ringing in the ears, severe increase in blood pressure, skin reactions caused by sunlight, tingling sensation, unusual headache with stiff neck (aseptic meningitis), vertigo, worsening of epilepsy.

These are not all the side effects reported with VIOXX. Do not use this leaflet alone for information about side effects. Your doctor or pharmacist can talk to you about other side effects. Any time you or your child have a medical problem you think may be related to VIOXX, talk to your doctor.

What is VIOXX used for?

VIOXX is used in adults for:

- relief of the pain and inflammation (swelling and soreness) of osteoarthritis (arthritis from wear and tear on your bones and your joints)
- relief of the pain and inflammation of rheumatoid arthritis in adults (arthritis caused by a condition where your immune system attacks your joints)
- management of short-term pain
- treatment of menstrual pain (pain during women's monthly periods)
- treatment of migraine headache attacks with or without aura.

VIOXX is used in children and adolescents, of at least 2 years of age and who weigh at least 10 kg (22 lbs.) to help relieve:

- the signs and symptoms of pauciarticular or polyarticular Juvenile Rheumatoid Arthritis (JRA). VIOXX has not been studied in children with systemic type JRA.

VIOXX has not been studied in children less than 2 years old or with body weight less than 10 kg (22 lbs.).

What should I tell my doctor before and during treatment with VIOXX?

Tell your doctor about all your or your child's medical conditions including if you or your child have or have had:

- an allergic reaction to aspirin or other NSAIDs
- asthma (a small number of patients with asthma have reactions to aspirin or other NSAIDs)
- stomach problems such as ulcers or bleeding
- kidney disease
- liver disease
- angina (for instance, chest, arm, or jaw pain), a heart attack, or a blocked artery in the heart
- heart failure
- high blood pressure

Tell your doctor if you or your child are:

- pregnant or plan to become pregnant. VIOXX may harm your unborn baby if you take it in late pregnancy. If you take VIOXX while you are pregnant, ask your doctor how you can be on the VIOXX Pregnancy Registry.
- breast-feeding or plan to breast-feed. It is not known if VIOXX passes into your milk and if it can harm your baby. You should discuss with your doctor whether or not to take VIOXX if you are breast-feeding.

Tell your doctor about:

- any other medical problems or allergies you or your child have now or have had.
- all the medicines you or your child take including prescription and non-prescription medicines, vitamins, and herbal supplements.

Tell your doctor right away if you or your child develop:

- serious stomach problems such as ulcer or bleeding symptoms (for instance, stomach burning, vomiting blood, or if there is blood in your bowel movement or it is black and sticky like tar).
- unexplained weight gain or swelling of the legs, feet, and/or hands.
- skin rash or allergic reactions. If you or your child have a severe allergic reaction, get medical help right away.

Can VIOXX be taken with other medicines?

Tell your doctor about all of the other medicines you or your child are taking or plan to take while you or your child are on VIOXX, even other medicines that you can get without a prescription, including vitamins and herbal supplements. VIOXX and certain other medicines can affect each other causing serious side effects. Keep a list of the medicines you or your child take. Show the list to your doctors and pharmacists each time you get a new medicine. They will tell you if it is safe to take VIOXX with other medicines. Especially tell your doctor if you or your child are taking:

- or have taken warfarin (Coumadin®) or any other similar blood thinner within the past 10 days
- theophylline (a medicine used to treat asthma)
- rifampin (an antibiotic)
- ACE inhibitors (medicines used for high blood pressure and heart failure)
- lithium (a medicine used to treat a certain type of depression).

VIOXX cannot take the place of aspirin for prevention of heart attack or stroke. If you or your child take both aspirin and VIOXX, there may be a higher chance of serious stomach problems than if VIOXX is taken alone. If you or your child are taking aspirin for prevention of heart attack or stroke, you or your child should not stop taking aspirin without talking to your doctor.

How should VIOXX be taken?

- Take VIOXX exactly as prescribed by the doctor. The dose will depend on the condition being treated and other medical problems you or your child may have. Do not change the dose of VIOXX or take extra doses unless the doctor has told you to.

- VIOXX may be taken with or without food.
- If you or your child miss a dose of VIOXX by a few hours, take it as soon as you remember. If it is close to the next dose, do NOT take the missed dose.
- If you or your child take too much VIOXX, call the doctor, pharmacist, or poison control center right away.

How should I store VIOXX?

- Store VIOXX at room temperature, 59° to 86°F (15° to 30°C).
- Safely throw away VIOXX that is out of date or no longer needed.
- Keep VIOXX and all medicines out of the reach of children.

What else should I know about VIOXX?

This leaflet provides a summary of certain information about VIOXX. If you have any questions or concerns about VIOXX talk to your health professional. Your doctor or pharmacist can give you an additional leaflet that is written for health professionals. This leaflet is also available at www.vioxx.com.

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use VIOXX for a condition for which it was not prescribed. Do not give VIOXX to other people even if they have the same symptoms you have. It may harm them.

What are the ingredients in VIOXX?

Active Ingredient: rofecoxib

Inactive Ingredients:

Oral suspension: citric acid (monohydrate), sodium citrate (dihydrate), sorbitol solution, strawberry flavor, xanthan gum, sodium methylparaben, sodium propylparaben.

Tablets: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide.

Rx Only

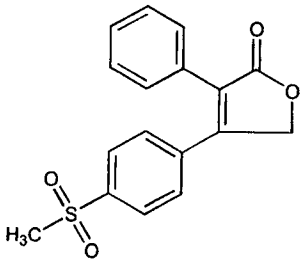
Issued August 2004

MERCK & CO., Inc.
Whitehouse Station, NJ 08889, USA

VIOXX®
(rofecoxib tablets and oral suspension)

DESCRIPTION

VIOXX* (rofecoxib) is described chemically as 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(*5H*)-furanone. It has the following chemical structure:



Rofecoxib is a white to off-white to light yellow powder. It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water. The empirical formula for rofecoxib is $C_{17}H_{14}O_4S$, and the molecular weight is 314.36.

Each tablet of VIOXX for oral administration contains either 12.5 mg, 25 mg, or 50 mg of rofecoxib and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide. The 50 mg tablets also contain red ferric oxide.

Each 5 mL of the oral suspension contains either 12.5 or 25 mg of rofecoxib and the following inactive ingredients: citric acid (monohydrate), sodium citrate (dihydrate), sorbitol solution, strawberry flavor, xanthan gum, and purified water. Added as preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

CLINICAL PHARMACOLOGY

Mechanism of Action

VIOXX is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. Studies to elucidate the mechanism of action of VIOXX in the acute treatment of migraine have not been conducted.

Pharmacokinetics

Absorption

The mean oral bioavailability of VIOXX at therapeutically recommended doses of 12.5, 25, and 50 mg is approximately 93%. The area under the curve (AUC) and peak plasma level (C_{max}) following a single 25-mg dose were 3286 (±843) ng•hr/mL and 207 (±111) ng/mL, respectively. Both C_{max} and AUC are roughly dose proportional across the clinical dose range. At doses greater than 50 mg, there is a less than proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. The plasma concentration-time profile exhibited multiple peaks. The median time to maximal concentration (T_{max}), as assessed in nine pharmacokinetic studies, is 2 to 3 hours. Individual T_{max} values in these studies ranged between 2 to 9 hours. This may not reflect rate of absorption as T_{max} may occur as a secondary peak in some individuals. With multiple dosing, steady-state conditions are reached by Day 4. The $AUC_{0\text{-}24hr}$ and C_{max} at steady state after multiple doses of 25 mg rofecoxib was 4018 (±1140) ng•hr/mL and 321 (±104) ng/mL, respectively, in healthy adults. The accumulation factor based on geometric means was 1.67. The $AUC_{0\text{-}24hr}$ and C_{max} at steady state after multiple doses of 25 mg rofecoxib was 6934 (±2158) ng•hr/mL and 519 (±163) ng/mL, respectively, in adult RA patients (N=12, mean body weight 62 kg).

---

*Registered trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey, USA

VIOXX Tablets 12.5 mg and 25 mg are bioequivalent to VIOXX Oral Suspension 12.5 mg/5 mL and 25 mg/5 mL, respectively.

Food and Antacid Effects

Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of rofecoxib when VIOXX Tablets were taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1 to 2 hours. The food effect on the suspension formulation has not been studied. VIOXX tablets can be administered without regard to timing of meals.

There was a 13% and 8% decrease in AUC when VIOXX was administered with calcium carbonate antacid and magnesium/aluminum antacid to elderly subjects, respectively. There was an approximate 20% decrease in C_{max} of rofecoxib with either antacid.

Distribution

Rofecoxib is approximately 87% bound to human plasma protein over the range of concentrations of 0.05 to 25 mcg/mL. The apparent volume of distribution at steady state (V_{dss}) is approximately 91 L following a 12.5-mg dose and 86 L following a 25-mg dose.

Rofecoxib has been shown to cross the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Metabolism of rofecoxib is primarily mediated through reduction by cytosolic enzymes. The principal metabolic products are the cis-dihydro and trans-dihydro derivatives of rofecoxib, which account for nearly 56% of recovered radioactivity in the urine. An additional 8.8% of the dose was recovered as the glucuronide of the hydroxy derivative, a product of oxidative metabolism. The biotransformation of rofecoxib and this metabolite is reversible in humans to a limited extent (<5%). These metabolites are inactive as COX-1 or COX-2 inhibitors.

Cytochrome P450 plays a minor role in metabolism of rofecoxib. Inhibition of CYP 3A activity by administration of ketoconazole 400 mg daily does not affect rofecoxib disposition. However, induction of general hepatic metabolic activity by administration of the non-specific inducer rifampin 600 mg daily produces a 50% decrease in rofecoxib plasma concentrations. (Also see *Drug Interactions*.)

Excretion

Rofecoxib is eliminated predominantly by hepatic metabolism with little (<1%) unchanged drug recovered in the urine. Following a single radiolabeled dose of 125 mg, approximately 72% of the dose was excreted into the urine as metabolites and 14% in the feces as unchanged drug.

The plasma clearance after 12.5- and 25-mg doses was approximately 141 and 120 mL/min, respectively. Higher plasma clearance was observed at doses below the therapeutic range, suggesting the presence of a saturable route of metabolism (i.e., non-linear elimination). The effective half-life (based on steady-state levels) was approximately 17 hours.

Special Populations

Gender

The pharmacokinetics of rofecoxib are comparable in men and women.

Geriatric

After a single dose of 25 mg VIOXX in elderly subjects (over 65 years old) a 34% increase in AUC was observed as compared to the young subjects. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

Pediatric

The steady state pharmacokinetics of rofecoxib was evaluated in patients ≥ 2 years to ≤ 17 years of age who weigh more than 10 kg with pauciarticular and polyarticular course Juvenile Rheumatoid Arthritis (JRA). The apparent clearance after oral administration of rofecoxib in patients ≥ 12 years to ≤ 17 years of age was similar to that of healthy adults and higher than that of adult RA patients. The apparent clearance after oral administration of rofecoxib in patients ≥ 2 years to ≤ 11 years of age was less than that of adults and increased with age. The apparent oral clearance of rofecoxib increases with body weight (and body surface area). (See Table 1.)

Table 1
Rofecoxib Apparent Oral Clearance (CL/F, mean ± SD) in JRA Patients* and Adults.

	JRA patients			Adults	
Group	2- to 5-year-old (N=21)	6- to 11-year-old (N=13)	12- to 17-year-old (N=11)	Healthy Age range: 20-48 (N=26)	RA Patients Age range: 31-64 (N=12)

Body Weight (kg) (mean ± SD)	17 ± 2	29 ± 6	57 ± 13	77 ± 13	62 ± 11
CL/F (mL/min)	37 ± 15	52 ± 13	87 ± 21	96 ± 30	65 ± 20

* Pauciarticular and Polyarticular Course JRA

A dose of 0.6 mg/kg to a maximum of 25 mg once daily in patients ≥ 2 years to ≤ 11 years of age and body weight 10 kg or above and a dose of 25 mg once daily in patients ≥ 12 years to ≤ 17 years of age would yield an AUC slightly higher than that of the 25-mg tablet once daily in healthy adults (AUC Geometric Mean Ratio, 1.12) and slightly lower than that in adult RA patients (AUC GMR, 0.77).

Race

Meta-analysis of pharmacokinetic studies has suggested a slightly (10-15%) higher AUC of rofecoxib in Blacks and Hispanics as compared to Caucasians. No dosage adjustment is necessary on the basis of race.

Hepatic Insufficiency

A single-dose pharmacokinetic study in mild (Child-Pugh score ≤6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. A pharmacokinetic study in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency indicated that mean rofecoxib plasma concentrations were higher (mean AUC: 55%; mean C_{max}: 53%) relative to healthy subjects. Since patients with hepatic insufficiency are prone to fluid retention and hemodynamic compromise, the maximum recommended chronic dose of VIOXX for patients with moderate hepatic insufficiency is 12.5 mg daily. (See PRECAUTIONS, *Hepatic Effects* and DOSAGE AND ADMINISTRATION, *Hepatic Insufficiency*.) Patients with severe hepatic insufficiency have not been studied.

Renal Insufficiency

In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While renal insufficiency does not influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is not recommended. (See WARNINGS, *Advanced Renal Disease*.)

Drug Interactions (Also see PRECAUTIONS, *Drug Interactions*.)

General

In human studies the potential for rofecoxib to inhibit or induce CYP 3A4 activity was investigated in studies using the intravenous erythromycin breath test and the oral midazolam test. No significant difference in erythromycin demethylation was observed with rofecoxib (75 mg daily) compared to placebo, indicating no induction of hepatic CYP 3A4. A 30% reduction of the AUC of midazolam was observed with rofecoxib (25 mg daily). This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP 3A4 by rofecoxib. *In vitro* studies in rat hepatocytes also suggest that rofecoxib might be a mild inducer for CYP 3A4.

Drug interaction studies with the recommended doses of rofecoxib have identified potentially significant interactions with rifampin, theophylline, and warfarin. Patients receiving these agents with VIOXX should be appropriately monitored. Drug interaction studies do not support the potential for clinically important interactions between antacids or cimetidine with rofecoxib. Similar to experience with other nonsteroidal anti-inflammatory drugs (NSAIDs), studies with rofecoxib suggest the potential for interaction with ACE inhibitors. The effects of rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole, prednisone/prednisolone, oral contraceptives, and digoxin have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Adults

Osteoarthritis (OA)

VIOXX has demonstrated significant reduction in joint pain compared to placebo. VIOXX was evaluated for the treatment of the signs and symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of 6 to 86 weeks duration that enrolled approximately 3900 patients. In patients with OA, treatment with VIOXX 12.5 mg and 25 mg once daily resulted in improvement in patient and physician global assessments and in the WOMAC (Western Ontario and McMaster Universities) osteoarthritis questionnaire, including pain, stiffness, and functional measures of OA. In six studies of pain

accompanying OA flare, VIOXX provided a significant reduction in pain at the first determination (after one week in one study, after two weeks in the remaining five studies); this continued for the duration of the studies. In all OA clinical studies, once daily treatment in the morning with VIOXX 12.5 and 25 mg was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg, the effectiveness of VIOXX was shown to be comparable to ibuprofen 800 mg TID and diclofenac 50 mg TID for treatment of the signs and symptoms of OA. The ibuprofen studies were 6-week studies; the diclofenac studies were 12-month studies in which patients could receive additional arthritis medication during the last 6 months.

Rheumatoid Arthritis (RA)

VIOXX has demonstrated significant reduction of joint tenderness/pain and joint swelling compared to placebo. VIOXX was evaluated for the treatment of the signs and symptoms of RA in two 12-week placebo- and active-controlled clinical trials that enrolled a total of approximately 2,000 patients. VIOXX was shown to be superior to placebo on all primary endpoints (number of tender joints, number of swollen joints, patient and physician global assessments of disease activity). In addition, VIOXX was shown to be superior to placebo using the American College of Rheumatology 20% (ACR20) Responder Index, a composite of clinical, laboratory, and functional measures of RA. VIOXX 25 mg once daily and naproxen 500 mg twice daily showed generally similar effects in the treatment of RA. A 50-mg dose once daily of VIOXX was also studied; however, no additional efficacy was seen compared to the 25-mg dose.

Analgesia, including Dysmenorrhea

In acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea, VIOXX relieved pain that was rated by patients as moderate to severe. The analgesic effect (including onset of action) of a single 50-mg dose of VIOXX was generally similar to 550 mg of naproxen sodium or 400 mg of ibuprofen. In single-dose post-operative dental pain studies, the onset of analgesia with a single 50-mg dose of VIOXX occurred within 45 minutes. In a multiple-dose study of post-orthopedic surgical pain in which patients received VIOXX or placebo for up to 5 days, 50 mg of VIOXX once daily was effective in reducing pain. In this study, patients on VIOXX consumed a significantly smaller amount of additional analgesic medication than patients treated with placebo (1.5 versus 2.5 doses per day of additional analgesic medication for VIOXX and placebo, respectively).

Migraine with or without aura

The efficacy of VIOXX in the acute treatment of migraine headaches was demonstrated in two double-blind, placebo-controlled, outpatient trials. Doses of 25 and 50 mg were compared to placebo in the treatment of one migraine attack. A second dose of VIOXX was not allowed in either trial. In these controlled short-term studies, patients were predominantly female (88%) and Caucasian (84%), with a mean age of 40 years (range 18 to 78). Patients were instructed to treat a moderate to severe headache. Headache relief, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 2 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of relief was assessed for up to 24 hours postdose. Other medication, with the exception of NSAIDs (including COX-2 inhibitors) or combination medications that contained NSAIDs, was permitted from 2 hours after the dose of study medication. The frequency and time to use of additional medications were also recorded.

In both placebo-controlled trials, the percentage of patients achieving headache relief 2 hours after treatment was significantly greater among patients receiving VIOXX at all doses compared to those who received placebo (Table 2). There were no statistically significant differences between the 25- and the 50-mg dose groups in either trial.

Table 2
Percentage of Patients with Headache Relief (Mild or No Headache)
2 hours Following Treatment

Trial	VIOXX 25 mg	VIOXX 50 mg	Placebo
1	54%* (n=176)	57%* (n=187)	34% (n=175)
2	60%* (n=187)	62%* (n=188)	30% (n=187)

*p<0.0001 vs. placebo

Note that, in general, comparisons of results obtained in different clinical studies conducted under different conditions by different investigators with different samples of patients are ordinarily unreliable for purposes of quantitative comparison.

The estimated probability of achieving initial headache relief within 2 hours following treatment is depicted in Figure 1.

Figure 1
Estimated Probability of Achieving Initial Headache Relief within 2 Hours

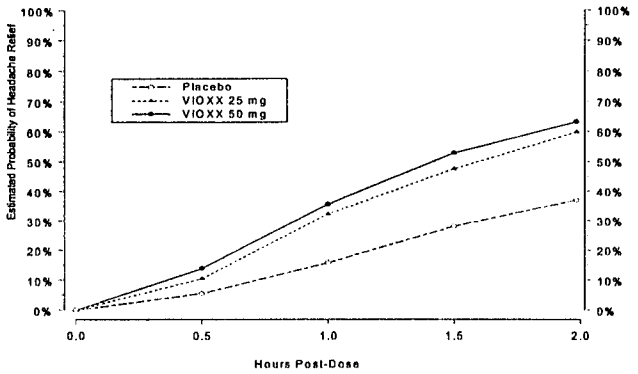
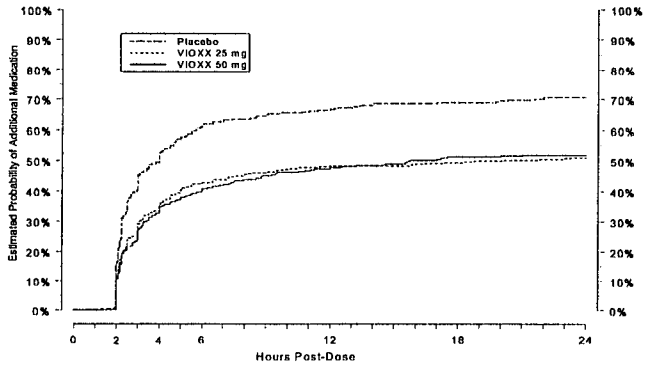


Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache relief (no or mild pain) following treatment with VIOXX or placebo. The plot is based on pooled data from the 2 placebo-controlled, outpatient trials in adults providing evidence of efficacy. Patients taking additional medication or not achieving headache relief prior to 2 hours were censored at 2 hours.

There was a decreased incidence of migraine-associated nausea, photophobia and phonophobia in VIOXX treated patients compared to placebo. The estimated probability of taking other medication for migraine over the 24 hours following initial dose of study treatment is summarized in Figure 2.

Figure 2
Estimated Probability of Patients Taking Additional Medication for Migraines
over the 24 Hours Following the Initial Dose of Study Treatment



This Kaplan-Meier plot is based on pooled data obtained in 2 placebo-controlled outpatient trials. Patients not using additional medications were censored at 24 hours. The plot includes both patients who had headache relief at 2 hours and those who had no response to the initial dose. Additional medication was not allowed within 2 hours postdose.

VIOXX was effective regardless of presence of aura, gender, race, age, presence of menses or dysmenorrhea. Similarly, the concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives did not affect efficacy. VIOXX was also effective whether or not there was a history of prior response to NSAIDs.

Special Studies

The following special studies were conducted to evaluate the comparative safety of VIOXX.

VIOXX GI Clinical Outcomes Research (VIGOR Study)

Study Design

The VIGOR study was designed to evaluate the comparative GI safety of VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) versus naproxen 500 mg twice daily (common therapeutic dose). The general safety and tolerability of VIOXX 50 mg once daily versus naproxen 500 mg twice daily was also studied. VIGOR was a randomized, double-blind study (median

duration of 9 months) in 8076 patients with rheumatoid arthritis (RA) requiring chronic NSAID therapy (mean age 58 years). Patients were not permitted to use concomitant aspirin or other antiplatelet drugs. Patients with a recent history of myocardial infarction or stroke and patients deemed to require low-dose aspirin for cardiovascular prophylaxis were to be excluded from the study. Fifty-six percent of patients used concomitant oral corticosteroids. The GI safety endpoints (confirmed by a blinded adjudication committee) included:

PUBs-symptomatic ulcers, upper GI perforation, obstruction, major or minor upper GI bleeding.

Complicated PUBs (a subset of PUBs)-upper GI perforation, obstruction or major upper GI bleeding.

Study Results

Gastrointestinal Safety in VIGOR

The VIGOR study showed a significant reduction in the risk of development of PUBs, including complicated PUBs in patients taking VIOXX compared to naproxen (see Table 3).

Table 3
VIGOR-Summary of Patients with Gastrointestinal Safety Events[1]
COMPARISON TO NAPROXEN

GI Safety Endpoints	VIOXX 50 mg daily (N=4047)[2] n[3] (Cumulative Rate[4])	Naproxen 1000 mg daily (N=4029)[2] n[3] (Cumulative Rate[4])	Relative Risk of VIOXX compared to naproxen[5]	95% CI[5]
PUBs	56 (1.80)	121 (3.87)	0.46*	(0.33, 0.64)
Complicated PUBs	16 (0.52)	37 (1.22)	0.43*	(0.24, 0.78)

[1]As confirmed by an independent committee blinded to treatment, [2]N=Patients randomized, [3]n=Patients with events, [4]Kaplan-Meier cumulative rate at end of study when at least 500 patients remained (approx. 10 1/2 months), [5]Based on Cox proportional hazard model

*p-value ≤0.005 for relative risk compared to naproxen

The risk reduction for PUBs and complicated PUBs for VIOXX compared to naproxen (approximately 50%) was maintained in patients with or without the following risk factors for developing a PUB (Kaplan-Meier cumulative rate of PUBs at approximately 10 1/2 months, VIOXX versus naproxen, respectively): with a prior PUB (5.12, 11.47); without a prior PUB (1.54, 3.27); age 65 or older (2.83, 6.49); or younger than 65 years of age (1.48, 3.01). A similar risk reduction for PUBs and complicated PUBs (approximately 50%) was also maintained in patients with or without *Helicobacter pylori* infection or concomitant corticosteroid use.

Other Safety Findings: Cardiovascular Safety

The VIGOR study showed a higher incidence of adjudicated serious cardiovascular thrombotic events in patients treated with VIOXX 50 mg once daily as compared to patients treated with naproxen 500 mg twice daily (see Table 4). This finding was largely due to a difference in the incidence of myocardial infarction between the groups. (See Table 5.) (See PRECAUTIONS, *Cardiovascular Effects.*) Adjudicated serious cardiovascular events (confirmed by a blinded adjudication committee) included: sudden death, myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack and peripheral venous and arterial thromboses.

Table 4
VIGOR-Summary of Patients with Serious Cardiovascular Thrombotic Adverse Events[1] Over Time
COMPARISON TO NAPROXEN

Treatment Group	Patients Randomized		4 Months[2]	8 Months[3]	10 ½ months[4]
VIOXX 50 mg	4047	Total number of events	17	29	45
		Cumulative Rate†	0.46%	0.82%	1.81%*
Naproxen 1000 mg	4029	Total number of events	9	15	19

Cumulative Rate†	0.23%	0.43%	0.60%

[1]Confirmed by blinded adjudication committee, [2]Number of patients remaining after 4 months were 3405 and 3395 for VIOXX and naproxen respectively, [3]Number of patients remaining after 8 months were 2806 and 2798 for VIOXX and naproxen respectively, [4]Number of patients remaining were 531 and 514 for VIOXX and naproxen respectively.

†Kaplan-Meier cumulative rate.

* p-value <0.002 for the overall relative risk compared to naproxen by Cox proportional hazard model

Table 5
VIGOR- Serious Cardiovascular Thrombotic Adverse Events [1]

	VIOXX 50 mg N[2]=4047 n[3]	Naproxen 1000 mg N[2]=4029 n[3]
Any CV thrombotic event	45 *	19
Cardiac events	28**	10
Fatal MI/Sudden death	5	4
Non-fatal MI	18**	4
Unstable angina	5	2
Cerebrovascular	11	8
Ischemic stroke	9	8
TIA	2	0
Peripheral	6	1

[1]Confirmed by blinded adjudication committee, [2]N=Patients randomized, [3]n=Patients with events

* p-value <0.002 and ** p-value ≤0.006 for relative risk compared to naproxen by Cox proportional hazard model

For cardiovascular data from 2 long-term placebo-controlled studies, see PRECAUTIONS, *Cardiovascular Effects*.

Upper Endoscopy in Patients with Osteoarthritis and Rheumatoid Arthritis

The VIGOR study described above compared clinically relevant outcomes. Several studies summarized below have utilized scheduled endoscopic evaluations to assess the occurrence of asymptomatic ulcers in individual patients taking VIOXX or a comparative agent. The results of outcomes studies, such as VIGOR, are more clinically relevant than the results of endoscopy studies (see CLINICAL STUDIES, *Special Studies, VIGOR*).

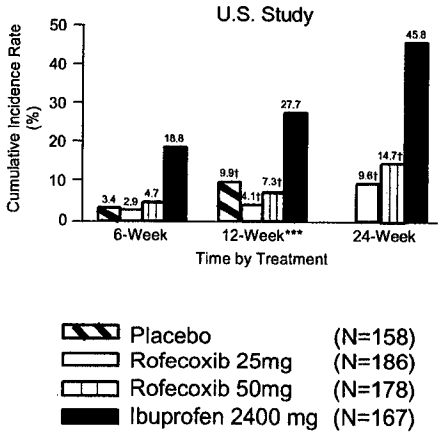
Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX 25 mg daily or 50 mg daily, ibuprofen 2400 mg daily, or placebo. Entry criteria for these studies permitted enrollment of patients with active *Helicobacter pylori* infection, baseline gastroduodenal erosions, prior history of an upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age ≥65 years. However, patients receiving aspirin (including low-dose aspirin for cardiovascular prophylaxis) were not enrolled in these studies. Patients who were 50 years of age and older with osteoarthritis and who had no ulcers at baseline were evaluated by endoscopy after weeks 6, 12, and 24 of treatment. The placebo-treatment group was discontinued at week 16 by design.

Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. See Figures 3 and 4 for the results of these studies.

Figure 3

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3 mm (Intention-to-Treat)**

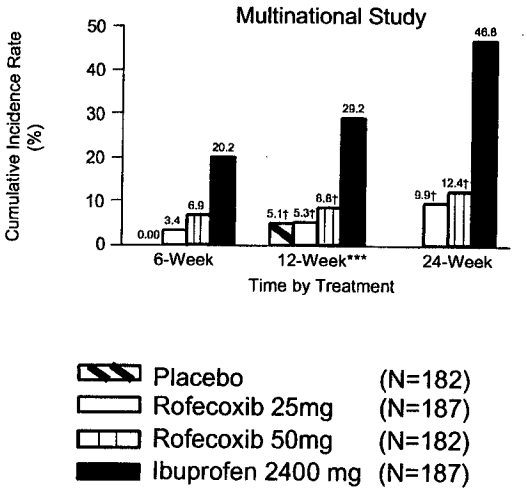


† p < 0.001 versus ibuprofen 2400 mg
** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.
*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

Figure 4

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3 mm (Intention-to-Treat)**



† p < 0.001 versus ibuprofen 2400 mg
** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.
*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

In a similarly designed 12-week endoscopy study in RA patients treated with VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) or naproxen 1000 mg daily (common therapeutic dose), treatment with VIOXX was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with naproxen.

A similarly designed 12-week endoscopy study was conducted in OA patients treated with low-dose enteric coated aspirin 81 mg daily, low-dose enteric coated aspirin 81 mg plus VIOXX 25 mg daily, ibuprofen 2400 mg daily, or placebo. There was no difference in the cumulative incidence of endoscopic gastroduodenal ulcers in patients taking low-dose aspirin plus VIOXX 25 mg as compared to those taking ibuprofen 2400 mg daily alone. Patients taking low-dose aspirin plus ibuprofen were not studied. (See PRECAUTIONS, *Drug Interactions, Aspirin.*)

Serious clinically significant upper GI bleeding has been observed in patients receiving VIOXX in controlled trials, albeit infrequently (see WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation*).

Assessment of Fecal Occult Blood Loss in Healthy Subjects

Occult fecal blood loss associated with VIOXX 25 mg daily, VIOXX 50 mg daily, ibuprofen 2400 mg per day, and placebo was evaluated in a study utilizing ^{51}Cr-tagged red blood cells in 67 healthy males. After 4 weeks of treatment with VIOXX 25 mg daily or VIOXX 50 mg daily, the increase in the amount of fecal blood loss was not statistically significant compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg per day produced a statistically significant increase in fecal blood loss as compared with placebo-treated subjects and VIOXX-treated subjects. The clinical relevance of this finding is unknown.

Platelets

Multiple doses of VIOXX 12.5, 25, and up to 375 mg administered daily up to 12 days had no effect on bleeding time relative to placebo. There was no inhibition of *ex vivo* arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25, and 50 mg of VIOXX.

Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. (See PRECAUTIONS, *Cardiovascular Effects.*)

Pediatric Patients

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

In a 12-week, double-blind active-controlled, non-inferiority study, 310 patients, 2 years to 17 years of age with pauciarticular or polyarticular course JRA, received the following treatments: lower-dose VIOXX 0.3 mg/kg (to a maximum of 12.5 mg) once daily in patients ≥ 2 years to ≤ 11 years of age or VIOXX 12.5 mg once daily in patients ≥ 12 years to ≤ 17 years of age; higher-dose VIOXX 0.6 mg/kg (to a maximum of 25 mg) once daily in patients ≥ 2 years to ≤ 11 years of age or VIOXX 25 mg once daily in patients ≥ 12 years to ≤ 17 years of age; NSAID comparator targeted to an effective dose in patients ≥ 2 years to ≤ 17 years of age. The response rates were based upon the JRA Definition of Improvement ≥ 30% (JRA DOI 30) criterion, which is a composite of clinical, laboratory, and functional measures of JRA. The JRA DOI 30 response rates were 55% in both the VIOXX 0.6 mg/kg (to a maximum of 25 mg) and NSAID comparator treatment groups achieving the non-inferiority criterion. A single non-inferiority trial is not sufficient to support a conclusion of equivalence.

In a 52-week open-label extension to the 12-week study, 160 patients received VIOXX 0.6 mg/kg to a maximum of 25 mg once daily (patients ≥ 2 years to ≤ 11 years of age) or 25 mg once daily (patients ≥ 12 years to ≤ 17 years of age) and 67 patients ≥ 2 years to ≤ 17 years of age received NSAID comparator targeted to an effective dose. There were no unexpected safety findings.

INDICATIONS AND USAGE

VIOXX is indicated:
For relief of the signs and symptoms of osteoarthritis.
For relief of the signs and symptoms of rheumatoid arthritis in adults.
For relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older and who weigh 10 kg (22 lbs) or more.
For the management of acute pain in adults.
For the treatment of primary dysmenorrhea.
For the acute treatment of migraine attacks with or without aura in adults.

The safety and effectiveness of VIOXX have not been established for cluster headache, which is present in an older, predominantly male, population.

with fatal outcome) have been reported with NSAIDs, including VIOXX. In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking rofecoxib (12.5 or 25 mg QD) and 0.1% of patients taking placebo had notable elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with VIOXX. The maximum recommended chronic daily dose in patients with moderate hepatic insufficiency is 12.5 mg daily. Use of VIOXX is not recommended in patients with severe hepatic insufficiency (see CLINICAL PHARMACOLOGY, *Special Populations* and DOSAGE AND ADMINISTRATION, *Hepatic Insufficiency*). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), VIOXX should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving VIOXX. In placebo-controlled trials, there were no significant differences observed between VIOXX and placebo in clinical reports of anemia. Patients on long-term treatment with VIOXX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. VIOXX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages (see CLINICAL STUDIES, *Special Studies, Platelets*).

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, VIOXX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients

Physicians should instruct their patients to read the patient package insert before starting therapy with VIOXX and to reread it each time the prescription is renewed in case any information has changed.

VIOXX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up. For additional gastrointestinal safety information see CLINICAL STUDIES, *Special Studies, VIGOR* and WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation*. Patients should be informed that VIOXX is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of effect on platelets. For additional cardiovascular safety information see CLINICAL STUDIES, *Special Studies, VIGOR* and PRECAUTIONS, *Cardiovascular Effects*.

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, edema or chest pain to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

Drug Interactions

ACE inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone. This interaction should be given consideration in patients taking VIOXX concomitantly with ACE inhibitors.

Aspirin: Concomitant administration of low-dose aspirin with VIOXX may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone. In a 12-week endoscopy study

conducted in OA patients there was no difference in the cumulative incidence of endoscopic gastroduodenal ulcers in patients taking low-dose (81 mg) enteric coated aspirin plus VIOXX 25 mg daily, as compared to those taking ibuprofen 2400 mg daily alone. Patients taking low-dose aspirin plus ibuprofen were not studied. (See CLINICAL STUDIES, *Special Studies, Upper Endoscopy in Patients with Osteoarthritis and Rheumatoid Arthritis*.)

At steady state, VIOXX 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by *ex vivo* platelet aggregation and serum TXB2 generation in clotting blood. Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. Therefore, in patients taking VIOXX, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis. (See CLINICAL STUDIES, *Special Studies, Platelets* and PRECAUTIONS, *Cardiovascular Effects*.) Prospective, long-term studies on concomitant administration of VIOXX and aspirin have not been conducted.

Cimetidine: Co-administration with high doses of cimetidine [800 mg twice daily] increased the C_{max} of rofecoxib by 21%, the $AUC_{0\text{-}120hr}$ by 23% and the $t_{1/2}$ by 15%. These small changes are not clinically significant and no dose adjustment is necessary.

Digoxin: Rofecoxib 75 mg once daily for 11 days does not alter the plasma concentration profile or renal elimination of digoxin after a single 0.5 mg oral dose.

Furosemide: Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Ketoconazole: Ketoconazole 400 mg daily did not have any clinically important effect on the pharmacokinetics of rofecoxib.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. In post-marketing experience there have been reports of increases in plasma lithium levels. Thus, when VIOXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: VIOXX 12.5, 25, and 50 mg, each dose administered once daily for 7 days, had no effect on the plasma concentration of methotrexate as measured by $AUC_{0\text{-}24hr}$ in patients receiving single weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. At higher than recommended doses, VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23% as measured by $AUC_{0\text{-}24hr}$ in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94%) and subsequently treated with methotrexate co-administered with 75 mg of rofecoxib (88%) had methotrexate plasma concentrations below the measurable limit (5 ng/mL). Standard monitoring of methotrexate-related toxicity should be continued if VIOXX and methotrexate are administered concomitantly.

Oral Contraceptives: Rofecoxib did not have any clinically important effect on the pharmacokinetics of ethinyl estradiol and norethindrone.

Prednisone/prednisolone: Rofecoxib did not have any clinically important effect on the pharmacokinetics of prednisolone or prednisone.

Rifampin: Co-administration of VIOXX with rifampin 600 mg daily, a potent inducer of hepatic metabolism, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, a starting daily dose of 25 mg of VIOXX should be considered for the treatment of osteoarthritis when VIOXX is co-administered with potent inducers of hepatic metabolism.

Theophylline: VIOXX 12.5, 25, and 50 mg administered once daily for 7 days increased plasma theophylline concentrations ($AUC_{(0\text{-}\infty)}$) by 38 to 60% in healthy subjects administered a single 300-mg dose of theophylline. Adequate monitoring of theophylline plasma concentrations should be considered when therapy with VIOXX is initiated or changed in patients receiving theophylline.

These data suggest that rofecoxib may produce a modest inhibition of cytochrome P450 (CYP) 1A2. Therefore, there is a potential for an interaction with other drugs that are metabolized by CYP 1A2 (e.g., amitriptyline, tacrine, and zileuton).

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing VIOXX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. In single and multiple dose studies in healthy subjects receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rofecoxib was not carcinogenic in mice given oral doses up to 30 mg/kg (male) and 60 mg/kg (female) (approximately 5- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) and in male and female rats given oral doses up to 8 mg/kg (approximately 6- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) for two years.

Rofecoxib was not mutagenic in an Ames test or in a V-79 mammalian cell mutagenesis assay, nor clastogenic in a chromosome aberration assay in Chinese hamster ovary (CHO) cells, in an *in vitro* and an *in vivo* alkaline elution assay, or in an *in vivo* chromosomal aberration test in mouse bone marrow.

Rofecoxib did not impair male fertility in rats at oral doses up to 100 mg/kg (approximately 20- and 7-fold human exposure at 25 and 50 mg daily based on the AUC_{0-24}) and rofecoxib had no effect on fertility in female rats at doses up to 30 mg/kg (approximately 19- and 7-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}).

Pregnancy

Teratogenic effects: Pregnancy Category C.

Rofecoxib was not teratogenic in rats at doses up to 50 mg/kg/day (approximately 28- and 10-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There was a slight, non-statistically significant increase in the overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day (approximately 1- or <1-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There are no studies in pregnant women. VIOXX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Rofecoxib produced peri-implantation and post-implantation losses and reduced embryo/fetal survival in rats and rabbits at oral doses ≥10 and ≥75 mg/kg/day, respectively (approximately 9- and 3-fold [rats] and 2- and <1-fold [rabbits] human exposure based on the AUC_{0-24} at 25 and 50 mg daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function. There was an increase in the incidence of postnatal pup mortality in rats at ≥5 mg/kg/day (approximately 5- and 2-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). In studies in pregnant rats administered single doses of rofecoxib, there was a treatment-related decrease in the diameter of the ductus arteriosus at all doses used (3-300 mg/kg: 3 mg/kg is approximately 2- and <1-fold human exposure at 25 or 50 mg daily based on AUC_{0-24}). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third trimester of pregnancy should be avoided.

Labor and delivery

Rofecoxib produced no evidence of significantly delayed labor or parturition in females at doses 15 mg/kg in rats (approximately 10- and 3-fold human exposure as measured by the AUC_{0-24} at 25 and 50 mg). The effects of VIOXX on labor and delivery in pregnant women are unknown.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to VIOXX while pregnant. Healthcare providers are encouraged to report any prenatal exposure to VIOXX by calling the **Pregnancy Registry at (800) 986-8999**.

Nursing mothers

Rofecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. There was an increase in pup mortality and a decrease in pup body weight following exposure of pups to milk from dams administered VIOXX during lactation. The dose tested represents an approximate 18- and 6-fold human exposure at 25 and 50 mg based on AUC_{0-24}. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VIOXX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The use of VIOXX in patients with pauciarticular or polyarticular course JRA ≥ 2 years to ≤ 17 years of age was studied in pharmacokinetic studies and a 12-week, double-blind active-controlled study with a 52-week open-label extension. (See CLINICAL PHARMACOLOGY, *Pediatric;* CLINICAL STUDIES, *Pediatric Patients, Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA);* ADVERSE REACTIONS, *Pauciarticular and Polyarticular Course JRA.*)

Rofecoxib has not been studied in patients under the age of 2 years, with body weight less than 10 kg (22 lbs.), or in children with systemic type JRA.

Geriatric Use

Of the patients who received VIOXX in osteoarthritis clinical trials, 1455 were 65 years of age or older. This included 460 patients who were 75 years or older, and in one of these studies, 174 patients who were 80 years or older. No substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. As with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

ADVERSE REACTIONS

Osteoarthritis

Approximately 3600 patients with osteoarthritis were treated with VIOXX; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. The following table of adverse experiences lists all adverse events, regardless of causality, occurring in at least 2% of patients receiving VIOXX in nine controlled studies of 6-week to 6-month duration conducted in patients with OA at the therapeutically recommended doses (12.5 and 25 mg), which included a placebo and/or positive control group.

Clinical Adverse Experiences occurring in ≥ 2.0% of Patients Treated with VIOXX in OA Clinical Trials

	Placebo	VIOXX 12.5 or 25 mg daily	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(N = 783)	(N = 2829)	(N = 847)	(N = 498)
Body As A Whole/Site Unspecified				
Abdominal Pain	4.1	3.4	4.6	5.8
Asthenia/Fatigue	1.0	2.2	2.0	2.6
Dizziness	2.2	3.0	2.7	3.4
Influenza-Like Disease	3.1	2.9	1.5	3.2
Lower Extremity Edema	1.1	3.7	3.8	3.4
Upper Respiratory Infection	7.8	8.5	5.8	8.2
Cardiovascular System				
Hypertension	1.3	3.5	3.0	1.6
Digestive System				
Diarrhea	6.8	6.5	7.1	10.6
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric Discomfort	2.8	3.8	9.2	5.4
Heartburn	3.6	4.2	5.2	4.6
Nausea	2.9	5.2	7.1	7.4
Eyes, Ears, Nose, And Throat				
Sinusitis	2.0	2.7	1.8	2.4
Musculoskeletal System				
Back Pain	1.9	2.5	1.4	2.8
Nervous System				
Headache	7.5	4.7	6.1	8.0
Respiratory System				
Bronchitis	0.8	2.0	1.4	3.2
Urogenital System				
Urinary Tract Infection	2.7	2.8	2.5	3.6

In the OA studies, the following spontaneous adverse events occurred in >0.1% to 1.9% of patients treated with VIOXX regardless of causality:

Body as a Whole: abdominal distension, abdominal tenderness, abscess, chest pain, chills, contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, fungal infection, infection, laceration, pain, pelvic pain, peripheral edema, postoperative pain, syncope, trauma, upper extremity edema, viral syndrome.

Cardiovascular System: angina pectoris, atrial fibrillation, bradycardia, hematoma, irregular heartbeat, palpitation, premature ventricular contraction, tachycardia, venous insufficiency.

Digestive System: acid reflux, aphthous stomatitis, constipation, dental caries, dental pain, digestive gas symptoms, dry mouth, duodenal disorder, dysgeusia, esophagitis, flatulence, gastric disorder, gastritis, gastroenteritis, hematochezia, hemorrhoids, infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting.

Eyes, Ears, Nose, and Throat: allergic rhinitis, blurred vision, cerumen impaction, conjunctivitis, dry throat, epistaxis, laryngitis, nasal congestion, nasal secretion, ophthalmic injection, otic pain, otitis, otitis media, pharyngitis, tinnitus, tonsillitis.

Immune System: allergy, hypersensitivity, insect bite reaction.

Metabolism and Nutrition: appetite change, hypercholesterolemia, weight gain.

Musculoskeletal System: ankle sprain, arm pain, arthralgia, back strain, bursitis, cartilage trauma, joint swelling, muscular cramp, muscular disorder, muscular weakness, musculoskeletal pain, musculoskeletal stiffness, myalgia, osteoarthritis, tendinitis, traumatic arthropathy, wrist fracture.

Nervous System: hypesthesia, insomnia, median nerve neuropathy, migraine, muscular spasm, paresthesia, sciatica, somnolence, vertigo.

Psychiatric: anxiety, depression, mental acuity decreased.

Respiratory System: asthma, cough, dyspnea, pneumonia, pulmonary congestion, respiratory infection.

Skin and Skin Appendages: abrasion, alopecia, atopic dermatitis, basal cell carcinoma, blister, cellulitis, contact dermatitis, herpes simplex, herpes zoster, nail unit disorder, perspiration, pruritus, rash, skin erythema, urticaria, xerosis.

Urogenital System: breast mass, cystitis, dysuria, menopausal symptoms, menstrual disorder, nocturia, urinary retention, vaginitis.

The following serious adverse events have been reported rarely (estimated <0.1%) in patients taking VIOXX, regardless of causality. Cases reported only in the post-marketing experience are indicated in italics.

Cardiovascular: cerebrovascular accident, congestive heart failure, deep venous thrombosis, *hypertensive crisis*, myocardial infarction, *pulmonary edema*, pulmonary embolism, transient ischemic attack, unstable angina.

Gastrointestinal: cholecystitis, colitis, colonic malignant neoplasm, *duodenal perforation*, duodenal ulcer, *esophageal ulcer*, *gastric perforation*, *gastric ulcer*, gastrointestinal bleeding, *hepatic failure*, *hepatitis*, intestinal obstruction, *jaundice*, pancreatitis.

Hemic and lymphatic: agranulocytosis, *aplastic anemia*, *leukopenia*, lymphoma, *pancytopenia*, *thrombocytopenia*.

Immune System: anaphylactic/anaphylactoid reaction, *angioedema*, *bronchospasm*, *hypersensitivity vasculitis*.

Metabolism and nutrition: hyponatremia.

Nervous System: aseptic meningitis, *epilepsy aggravated*.

Psychiatric: confusion, *hallucinations*.

Skin and Skin Appendages: photosensitivity reactions, severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Urogenital System: acute renal failure, breast malignant neoplasm, *hyperkalemia*, *interstitial nephritis*, prostatic malignant neoplasm, urolithiasis, *worsening chronic renal failure*.

In 1-year controlled clinical trials and in extension studies for up to 86 weeks (approximately 800 patients treated with VIOXX for one year or longer), the adverse experience profile was qualitatively similar to that observed in studies of shorter duration.

Rheumatoid Arthritis

Approximately 1,100 patients were treated with VIOXX in the Phase III rheumatoid arthritis efficacy studies. These studies included extensions of up to 1 year. The adverse experience profile was generally similar to that reported in the osteoarthritis studies. In studies of at least three months, the incidence of hypertension in RA patients receiving the 25 mg once daily dose of VIOXX was 10.0% and the incidence of hypertension in patients receiving naproxen 500 mg twice daily was 4.7%.

Analgesia, including primary dysmenorrhea

Approximately one thousand patients were treated with VIOXX in analgesia studies. All patients in post-dental surgery pain studies received only a single dose of study medication. Patients in primary dysmenorrhea studies may have taken up to 3 daily doses of VIOXX, and those in the post-orthopedic surgery pain study were prescribed 5 daily doses of VIOXX.

The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies. The following additional adverse experience, which occurred at an incidence of at least 2% of patients treated with VIOXX, was observed in the post-dental pain surgery studies: post-dental extraction alveolitis (dry socket).

Migraine with or without aura

Approximately 750 patients were treated with a single dose of VIOXX 25 mg or 50 mg in two single-attack migraine studies. Approximately 460 patients in the 3-month extension phase of one study treated up to 8 (average 3) migraine attacks per month. In single attack studies, the following adverse events were more frequent in the VIOXX treatment groups (25 mg and 50 mg) compared to the placebo group, and occurred at an incidence of at least 2% of patients treated: dizziness, nausea, somnolence and dyspepsia. In the 3-month extension phase of one study, the following adverse events occurred at an incidence of at least 2% of patients treated in the VIOXX treatment groups (25 mg and 50 mg): dizziness, dry mouth, nausea, and vomiting.

Clinical Studies in OA and RA with VIOXX 50 mg (Twice the highest dose recommended for chronic use)

In OA and RA clinical trials which contained VIOXX 12.5 or 25 mg as well as VIOXX 50 mg, VIOXX 50 mg QD was associated with a higher incidence of gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea and vomiting), lower extremity edema, hypertension, serious* adverse experiences and discontinuation due to clinical adverse experiences compared to the recommended chronic doses of 12.5 and 25 mg (see DOSAGE AND ADMINISTRATION).

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis

In a 12-week study, 209 JRA patients, ≥ 2 years to ≤ 17 years of age, were treated with rofecoxib; 109 and 100 patients were treated with lower-dose rofecoxib and higher-dose rofecoxib, respectively. In a 52-week open-label extension, 160 JRA patients, ≥ 2 years to ≤ 17 years of age, were treated with higher-dose rofecoxib for up to 15 months. No new adverse experiences were identified other than a single case of pseudoporphyria (a photo-induced blistering reaction), an adverse event that has been seen in patients with JRA treated with non-selective NSAIDs. In this 12-week study, the most common adverse experiences (at 0.6 mg/kg dose) were upper abdominal pain, nasopharyngitis, diarrhea, upper respiratory tract infection, abdominal pain, headache and rhinitis. Rash was also reported.

OVERDOSAGE

No overdoses of VIOXX were reported during clinical trials. Administration of single doses of VIOXX 1000 mg to 6 healthy volunteers and multiple doses of 250 mg/day for 14 days to 75 healthy volunteers did not result in serious toxicity.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

Rofecoxib is not removed by hemodialysis; it is not known whether rofecoxib is removed by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

VIOXX is administered orally. The lowest dose of VIOXX should be sought for each patient.

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Rheumatoid Arthritis

The recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg.

*adverse experience that resulted in death, permanent or substantial disability, hospitalization, congenital anomaly, or cancer, was immediately life threatening, was due to an overdose, or was thought by the investigator to require intervention to prevent one of the above outcomes

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis

Pediatric Patients	Daily Dose
≥ 2 years to ≤ 11 years of age and ≥ 10 to < 42 kg	0.6 mg/kg to a maximum of 25 mg*
≥ 2 years to ≤ 11 years of age and ≥ 42 kg	25 mg
≥ 12 years to ≤ 17 years of age	25 mg

*Oral suspension dosage form is recommended. To improve dosing accuracy in smaller weight children, the use of 12.5 mg/5 mL oral suspension (2.5 mg/mL) is recommended.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of VIOXX is 50 mg once daily. The maximum recommended daily dose is 50 mg. Use of VIOXX for more than 5 days in management of pain has not been studied. Chronic use of VIOXX 50 mg daily is not recommended. (See ADVERSE REACTIONS, *Clinical Studies in OA and RA with VIOXX 50 mg*).

Acute Treatment of Migraine Attacks with or without aura

The recommended starting dose of VIOXX is 25 mg once daily. Some patients may receive additional benefit with 50 mg as compared to 25 mg. The maximum recommended daily dose is 50 mg. The safety of treating more than 5 migraine attacks in any given month has not been established. Chronic daily use of VIOXX for the acute treatment of migraine is not recommended.

Hepatic Insufficiency

Because of significant increases in both AUC and C_{max} in patients with moderate hepatic impairment (Child-Pugh score: 7-9), the maximum recommended chronic daily dose is 12.5 mg. (See CLINICAL PHARMACOLOGY, *Special Populations*). The efficacy of 12.5 mg in rheumatoid arthritis patients with moderate hepatic insufficiency has not been studied.

VIOXX Tablets may be taken with or without food.

Oral Suspension

VIOXX Oral Suspension 12.5 mg/5 mL or 25 mg/5 mL may be substituted for VIOXX Tablets 12.5 or 25 mg, respectively, in any of the above indications. Shake before using.

HOW SUPPLIED

No. 3810 — Tablets VIOXX, 12.5 mg, are cream/off-white, round, shallow cup tablets engraved MRK 74 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0074-31 unit of use bottles of 30
NDC 0006-0074-28 unit dose packages of 100
NDC 0006-0074-68 bottles of 100
NDC 0006-0074-82 bottles of 1000
NDC 0006-0074-80 bottles of 8000.

No. 3834 — Tablets VIOXX, 25 mg, are yellow, round tablets engraved MRK 110 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0110-31 unit of use bottles of 30
NDC 0006-0110-28 unit dose packages of 100
NDC 0006-0110-68 bottles of 100
NDC 0006-0110-82 bottles of 1000
NDC 0006-0110-80 bottles of 8000.

No. 3835 — Tablets VIOXX, 50 mg, are orange, round tablets engraved MRK 114 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0114-31 unit of use bottles of 30
NDC 0006-0114-28 unit dose packages of 100
NDC 0006-0114-68 bottles of 100
NDC 0006-0114-74 bottles of 500
NDC 0006-0114-81 bottles of 4000.

No. 3784 — Oral Suspension VIOXX, 12.5 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3784-64 unit of use bottles containing 150 mL (12.5 mg/5 mL).

No. 3785 — Oral Suspension VIOXX, 25 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3785-64 unit of use bottles containing 150 mL (25 mg/5 mL).

Storage
VIOXX Tablets:
Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]
VIOXX Oral Suspension:
Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

Rx only

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued August 2004
Printed in USA

Vioxx Timeline

VIOXX TIMELINE
Key Dates for VIGOR and Long-term, Placebo-controlled Studies Implemented to Provide Cardiovascular Safety Data

1993	Studies published in which indobufen (Circulation, 1993, 87:162-164) and the non-selective NSAID flurbiprofen (European Heart Journal, 1993, 13, 951-957) are shown to reduce cardiovascular (cv) events.
1998	
April	Results of FitzGerald study first presented. Among the results of the study was the surprising discovery that COX-2 specific inhibitors reduced the urinary excretion of prostacyclin metabolite. Based on these results, it was, for the first time, hypothesized that COX-2 specific inhibitors may alter the balance between prostacyclin and thromboxane and thereby increase the risk of cv events.
	Trial of VIOXX versus placebo in the prevention of Alzheimer's in patients with Mild Cognitive Impairment (MCI) begins.
Nov	Vioxx New Drug Application (NDA) submitted to the U.S. Food & Drug Administration (FDA). The application included data on approximately 5,400 osteoarthritis patients who participated in 8 double-blind, placebo-controlled and active-comparator studies. In these studies, similar rates of investigator-reported thrombotic cardiovascular adverse events were seen with VIOXX, placebo, and comparator NSAIDs (ibuprofen, diclofenac, or nabumetone).
1999	
Jan	VIOXX Gastrointestinal Outcomes Research[1] (VIGOR) trial initiated.
Feb	First trial of VIOXX versus placebo for the treatment of Alzheimer's disease begins.
April	Public meeting of FDA Advisory Committee on VIOXX NDA.
May	VIOXX approved by the FDA.
Oct	Adenomatous Polyp Prevention On VIOXX[2] (APPROVe) trial protocol finalized.

2000

Feb	APPROVe trial enrollment begins.
March	Preliminary results from VIGOR become available to Merck.
March	News release on preliminary results of VIGOR issued by Merck.
March	Preliminary VIGOR results submitted to the FDA.
March	Merck unblinded to safety data from two ongoing Alzheimer's studies – one for prevention and one for treatment – that compare VIOXX to placebo. These data show no difference in cardiovascular event rates between VIOXX and placebo.
April	Second trial of VIOXX versus placebo for the treatment of Alzheimer's begins.
May	Preliminary VIGOR data submitted to the *New England Journal of Medicine* for publication.
May	VIGOR presented at Digestive Disease Week.
June	Final VIGOR data submitted to FDA in a Supplemental New Drug Application, which included draft prescribing information.
Nov	The GI and cardiovascular safety findings from VIGOR published in *The New England Journal of Medicine*.
	First VIOXX versus placebo trial in the treatment of Alzheimer's disease ends.
	In preparation for VIGOR Advisory Committee, second interim analysis of safety data from Alzheimer's prevention and treatment trials conducted, again showing no difference in cardiovascular event rates between VIOXX and placebo.

2001

Feb	Public meeting of FDA Advisory Committee on VIGOR.
May	Second trial of VIOXX versus placebo for treatment Alzheimer's disease stopped.
Oct	Pooled analysis of cardiovascular data from Phase II/III studies published in Circulation. Analysis demonstrated that VIOXX was not associated with excess cardiovascular thrombotic events compared with either placebo or non-naproxen NSAIDs.
Sept	Merck and Oxford University sign letter of intent to conduct the VIOXX in Colorectal Cancer Therapy: definition of Optimal Therapy[3] (VICTOR) trial.
Nov	APPROVe enrollment completed.

2002

April	U.S. Prescribing Information for VIOXX updated with VIGOR information and data from two placebo-controlled studies
April	First patient is enrolled in VICTOR trial.
June	Pooled analysis of placebo-controlled studies in patients with Alzheimer's and MCI presented at EULAR. The incidence of

serious cardiovascular adverse events in this population was similar on VIOXX and placebo.

2003

March	VIOXX in Prostate cancer (ViP) trial protocol finalized.
April	Trial of VIOXX versus placebo in MCI ends.
June	ViP trial enrollment begins.
	Updated pooled analysis of Alzheimer's treatment and MCI data presented at EULAR. The cardiovascular event rate in patients taking VIOXX 25 mg continued to be similar to the rate in patients taking placebo; mean duration of treatment was 1.2 years in VIOXX group and 1.3 years in placebo group.
Oct	Updated pooled analysis published in the American Heart Journal. Analysis demonstrated that VIOXX was not associated with excess cv thrombotic events compared with either placebo or non-naproxen NSAIDs.

2004

Sept	APPROVe External Data Safety Monitoring Board notifies Merck of its recommendation to end APPROVe trial.
Sept	APPROVe, ViP and VICTOR trials terminated early.
Sept	Merck voluntarily withdraws VIOXX from the market.
Nov	APPROVe trial scheduled to end.

2005

Aug	ViP trial enrollment scheduled to be completed.

2011

Aug	ViP trial scheduled to end.

---

1. In VIGOR, Vioxx 50 mg once daily (n=4,047) – a dose twice the highest recommended chronic dose -- was compared to a common therapeutic dose of naproxen 500 mg twice daily (n=4,029) in patients with rheumatoid arthritis (median length of participation was nine months). The study assessed the incidence of serious GI events and the most serious, or "complicated," GI events, which included perforations, obstructions or major bleeding (PUB) in the upper GI tract. The study was designed to exclude patients requiring aspirin for cardioprotection.

In VIGOR, Vioxx 50 mg once daily significantly reduced the risk of serious GI events by 54 percent and the risk of complicated GI events by 57 percent compared to naproxen 500 mg twice daily. A total of 56 patients treated with Vioxx experienced a serious GI event compared to 121 patients taking naproxen, and a total of 16 patients receiving Vioxx had a complicated GI event versus 37 patients taking naproxen. In the study, the reduction in risk for serious and complicated GI events with Vioxx was maintained in patients both at high risk for developing a PUB and in patients without risk factors. Such

risk factors include: prior history of a PUB, age of 65 or older, *Helicobacter pylori* infectionor concomitant use of corticosteroids.

In VIGOR, a statistically significant higher incidence of serious cardiovascular thrombotic events was seen in patients receiving Vioxx 50 mg once daily compared to patients treated with naproxen 500 mg twice daily. A total of 45 serious cardiovascular thrombotic events occurred among 4,047 patients taking Vioxx compared to 19 among 4,029 taking naproxen. This was largely due to a difference in the incidence of non-fatal heart attacks: 18 for Vioxx and 4 for naproxen. The number of cardiovascular thrombotic deaths was similar in patients treated with Vioxx (n=7) compared to naproxen (n=6).

2. APPROVe was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (3 years) of treatment with rofecoxib on the recurrence of adenomatous polyps of the large bowel in patients with a history of colorectal adenomas. The study included approximately 2600 patients aged 40-96; approximately 62% male. Aspirin was allowed in the study.

In APPROVe there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment for patients taking VIOXX as compared to placebo. Results for the first 18 months of the study did not show an increased risk of confirmed CV events on VIOXX and in this respect, the results are similar to the results of two prior placebo controlled studies described in the current U.S. labeling for VIOXX.

Merck followed the recommendation of the study's External Safety Monitoring Board and terminated this trial on September 30, 2004.

3. VICTOR was a randomized, double-blind, placebo-controlled, international, multicenter study of VIOXX in 7,000 colorectal cancer patients following potentially curative therapy. The primary hypothesis tested in the study was that VIOXX administered for two years will result in greater overall survival compared with placebo. CV events were monitored by the VICTOR trial investigators and Merck as part of the adverse events monitoring conducted as part of the study. The study was stopped on September 30, 2004.

4. ViP was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the effects of VIOXX in decreasing the risk of prostate cancer. The study protocol called for 15,000 male patients, aged = 50 and = 75 years, with a life expectancy of greater than 6 years, with PSA = 2.5 ng/mL and = 10 ng/mL to be enrolled. The primary hypothesis to be tested in the study was that the risk of developing prostate cancer over six years of treatment will be lower in patients treated with VIOXX 25 mg/day than in patients treated with placebo; and that treatment with VIOXX would be generally safe and well tolerated. Cardiovascular adverse events were monitored by an external safety monitoring board as a part of the study. The trial was halted on September 30, 2004.

###

Forward-Looking Statement

This document contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the cautionary statements in Item 1 of Merck's Form 10-K for the year ended Dec. 31, 2003, and in its periodic reports on Form 10-Q and Form 8-K (if any) which the company incorporates by reference.

Prescription Drug User Fee Act

Prescription Drug User Fee Amendments of 2002

Subtitle <<NOTE: Prescription Drug User Fee Amendments of 2002.>> A--Prescription Drug User Fees

SEC. 501. <<NOTE: 21 USC 301 note.>> SHORT TITLE.

This subtitle may be cited as the ``Prescription Drug User Fee Amendments of 2002''.

SEC. 502. <<NOTE: 21 USC 379g note.>> FINDINGS.

The Congress finds that--

(1) prompt approval of safe and effective new drugs and other therapies is critical to the improvement of the public health so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease;

(2) the public health will be served by making additional funds available for the purpose of augmenting the resources of the Food and Drug Administration that are devoted to the process for the review of human drug applications and the assurance of drug safety;

(3) the provisions added by the Prescription Drug User Fee Act of 1992, as amended by the Food and Drug Administration Modernization Act of 1997, have been successful in substantially reducing review times for human drug applications and should be--

(A) reauthorized for an additional 5 years, with certain technical improvements; and

(B) carried out by the Food and Drug Administration with new commitments to implement more ambitious and comprehensive improvements in regulatory processes of the Food and Drug Administration, including--

(i) strengthening and improving the review and monitoring of drug safety;

(ii) considering greater interaction between the agency and sponsors during the review of drugs and biologics intended to treat serious diseases and life-threatening diseases; and

(iii) developing principles for improving first-cycle reviews; and

(4) the fees authorized by amendments made in this subtitle will be dedicated towards expediting the drug development process and the process for the review of human drug applications as set forth in the goals identified for purposes of part 2 of subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act, in the letters from the Secretary of Health and Human Services to the chairman of the Committee on Energy and Commerce of the House of Representatives and the chairman of the Committee on Health, Education, Labor and Pensions of the Senate, as set forth in the Congressional Record.

SEC. 503. DEFINITIONS.

Section 735 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379g) is amended--

(1) in paragraph (1), in the matter after and below subparagraph (C), by striking ``licensure, as described in

subparagraph (D)'' and inserting ``licensure, as described in subparagraph (C)'';

(2) in paragraph (3)--

(A) in subparagraph (A), by striking ``and'' at the end;

(B) in subparagraph (B), by striking the period and inserting ``, and'';

(C) by inserting after subparagraph (B) the following subparagraph:

``(C) which is on the list of products described in section 505(j)(7)(A) or is on a list created and maintained by the Secretary of products approved under human drug applications under section 351 of the Public Health Service Act.''; and

(D) in the matter after and below subparagraph (C) (as added by subparagraph (C) of this paragraph), by striking ``Service Act,'' and all that follows through ``biological product'' and inserting the following: ``Service Act. Such term does not include a biological product'';

(3) in paragraph (6), by adding at the end the following subparagraph:

``(F) In the case of drugs approved after October 1, 2002, under human drug applications or supplements: collecting, developing, and reviewing safety information on the drugs, including adverse event reports, during a period

[[Page 116 STAT. 689]]

of time after approval of such applications or supplements, not to exceed three years.''; and

(4) in paragraph (8)--

(A) by striking the matter after and below subparagraph (B);

(B) by striking subparagraph (B);

(C) by striking ``is the lower of'' and all that follows through ``Consumer Price Index'' and inserting ``is the Consumer Price Index''; and

(D) by striking ``1997, or'' and inserting ``1997.''.

SEC. 504. AUTHORITY TO ASSESS AND USE DRUG FEES.

(a) Types of Fees.--Section 736(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(a)) is amended--

(1) in the matter preceding paragraph (1), by striking ``fiscal year 1998'' and inserting ``fiscal year 2003'';

(2) in paragraph (1)(A)--

(A) in each of clauses (i) and (ii), by striking ``in subsection (b)'' and inserting ``under subsection (c)(4)''; and

(B) in clause (ii), by adding at the end the following sentence: ``Such fee shall be half of the amount of the fee established under clause (i).'';

(3) in paragraph (2)(A), in the matter after and below clause (ii)--

(A) by striking ``in subsection (b)'' and inserting ``under subsection (c)(4)''; and

(B) by striking ``payable on or before January 31''

and inserting ``payable on or before October 1''; and

(4) in paragraph (3)--

(A) by amending subparagraph (A) to read as follows:

``(A) In general.--Except as provided in subparagraph (B), each person who is named as the applicant in a human drug application, and who, after September 1, 1992, had pending before the Secretary a human drug application or supplement, shall pay for each such prescription drug product the annual fee established under subsection (c)(4). Such fee shall be payable on or before October 1 of each year. Such fee shall be paid only once for each product for a fiscal year in which the fee is payable.''; and

(B) in subparagraph (B), by striking ``The listing'' and all that follows through ``filed under section 505(b)(2)'' and inserting the following: ``A prescription drug product shall not be assessed a fee under subparagraph (A) if such product is identified on the list compiled under section 505(j)(7)(A) with a potency described in terms of per 100 mL, or if such product is the same product as another product approved under an application filed under section 505(b)''.

(b) Fee Amounts.--Section 736(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(b)) is amended to read as follows:

``(b) Fee Revenue Amounts.--Except as provided in subsections (c), (d), (f), and (g), fees under subsection (a) shall be established to generate the following revenue amounts:

``Type of Fee Revenue	Fiscal Year 2003	Fiscal Year 2004	Fiscal Year 2005
Application/Supplement	$74,300,000	$77,000,000	$84,000,000
Establishment	$74,300,000	$77,000,000	$84,000,000
Product	$74,300,000	$77,000,000	$84,000,000
Total Fee Revenue	$222,900,000	$231,000,000	$252,000,000

If, after the date of the enactment of the Prescription Drug User Fee Amendments of 2002, legislation is enacted requiring the Secretary to fund additional costs of the retirement of Federal personnel, fee revenue amounts shall be increased in each year by the amount necessary to fully fund the portion of such additional costs that are attributable to the process for the review of human drug applications.''.

(c) Adjustments.--Section 736(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(c)) is amended--

(1) in paragraph (1)--

(A) in the matter preceding subparagraph (A), by striking ``fees and total fee revenues'' and inserting ``revenues'';

(B) in subparagraph (A)--

(i) by striking ``during the preceding fiscal year''; and

(ii) by striking ``, or'' and inserting the following: ``for the 12 month period ending June 30 preceding the fiscal year for which fees are

being established, or'';

(C) in subparagraph (B), by striking ``for such fiscal year'' and inserting ``for the previous fiscal year''; and

(D) in the matter after and below subparagraph (B), by striking ``fiscal year 1997''; and inserting ``fiscal year 2003'';

(2) by redesignating paragraphs (2) and (3) as paragraphs (4) and (5), respectively;

(3) by inserting after paragraph (1) the following paragraphs:

``(2) <<NOTE: Effective date.>> Workload adjustment.--Beginning with fiscal year 2004, after the fee revenues established in subsection (b) are adjusted for a fiscal year for inflation in accordance with paragraph (1), the fee revenues shall be adjusted further for such fiscal year to reflect changes in the workload of the Secretary for the process for the review of human drug applications. With respect to such adjustment:

``(A) The adjustment shall be determined by the Secretary based on a weighted average of the change in the total number of human drug applications, commercial investigational new drug applications, efficacy supplements, and manufacturing supplements submitted to the Secretary. <<NOTE: Federal Register, publication.>> The Secretary shall publish in the Federal Register the fee revenues and fees resulting from the adjustment and the supporting methodologies.

``(B) Under no circumstances shall the adjustment result in fee revenues for a fiscal year that are less than the fee revenues for the fiscal year established in subsection (b), as adjusted for inflation under paragraph (1).

``(3) Final year adjustment.--For fiscal year 2007, the Secretary may, in addition to adjustments under paragraphs (1) and (2), further increase the fee revenues and fees established in subsection (b) if such an adjustment is necessary to provide for not more than three months of operating reserves of carryover user fees for the process for the review of human drug applications for the first three months of fiscal year 2008. If such an adjustment is necessary, the rationale for the amount of the increase shall be contained in the annual notice establishing fee revenues and fees for fiscal year 2007. If the Secretary has carryover balances for such process in excess of three months of such operating reserves, the adjustment under this paragraph shall not be made.''; and

(4) in paragraph (4) (as redesignated by paragraph (2) of this subsection), by amending such paragraph to read as follows:

``(4) <<NOTE: Effective date.>> Annual fee setting.--The Secretary shall, 60 days before the start of each fiscal year that begins after September 30, 2002, establish, for the next fiscal year, application, product, and establishment fees under subsection (a), based on the revenue amounts established under subsection (b) and the adjustments provided under this subsection.''.

(d) Fee Waiver or Reduction.--Section 736(d)) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(d)) is amended--

(1) in paragraph (1)--

(A) in subparagraph (C), by inserting ``or'' after the comma at the end;

(B) by striking subparagraph (D); and

(C) by redesignating subparagraph (E) as subparagraph (D); and

(2) in paragraph (3), in each of subparagraphs (A) and (B), by striking ``paragraph (1)(E)'' each place such term appears and inserting ``paragraph (1)(D)''.

(e) Assessment of Fees.--Section 736(f) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(f)) is amended--

(1) in the heading for the subsection, by striking ``Assessment of Fees.--'' and inserting ``Limitations.--''; and

(2) in paragraph (1), by striking the heading for the paragraph and all that follows through ``fiscal year beginning'' and inserting the following: ``In general.--Fees under subsection (a) shall be refunded for a fiscal year beginning''.

(f) Crediting and Availability of Fees.--

(1) In general.--Section 736(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(g)(1)) is amended by striking ``Fees collected for a fiscal year'' and all that follows through ``fiscal year limitation.'' and inserting the following: ``Fees authorized under subsection (a) shall be collected and available for obligation only to the extent and in the amount provided in advance in appropriations Acts. Such fees are authorized to remain available until expended.''.

(2) Collections and appropriation acts.--Section 736(g)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(g)(2)) is amended--

(A) by redesignating subparagraphs (A) and (B) as clauses (i) and (ii), respectively;

(B) by striking ``(2) Collections'' and all that follows through ``the amount specified'' in clause (i) (as so redesignated) and inserting the following:

``(2) Collections and appropriation acts.--

``(A) In general.--The fees authorized by this section--

``(i) shall be retained in each fiscal year in an amount not to exceed the amount specified'';

(C) by moving clause (ii) (as so redesignated) two ems to the right; and

(D) by adding at the end the following subparagraph:

``(B) Compliance.--The Secretary shall be considered to have met the requirements of subparagraph (A)(ii) in any fiscal year if the costs funded by appropriations and allocated for the process for the review of human drug applications--

``(i) are not more than 3 percent below the level specified in subparagraph (A)(ii); or

``(ii)(I) are more than 3 percent below the level specified in subparagraph (A)(ii), and fees assessed for the fiscal year following the subsequent fiscal year are decreased by the amount in excess of 3 percent by which such costs fell below the level specified in such subparagraph; and

``(II) such costs are not more than 5 percent below the level specified in such subparagraph.''.

(3) Authorization of appropriations.--Section 736(g)(3) of

the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(g)(3)) is amended by striking subparagraphs (A) through (E) and inserting the following:

``(A) $222,900,000 for fiscal year 2003;
``(B) $231,000,000 for fiscal year 2004;
``(C) $252,000,000 for fiscal year 2005;
``(D) $259,300,000 for fiscal year 2006; and
``(E) $259,300,000 for fiscal year 2007;''.

SEC. 505. <<NOTE: Effective dates. Deadlines. 21 USC 379g note.>> ACCOUNTABILITY AND REPORTS.

(a) Public Accountability.--

(1) Consultation.--In developing recommendations to the Congress for the goals and plans for meeting the goals for the process for the review of human drug applications for the fiscal years after fiscal year 2007, and for the reauthorization of sections 735 and 736 of the Federal Food, Drug, and Cosmetic Act, the Secretary of Health and Human Services (referred to in this section as the ``Secretary'') shall consult with the Committee on Energy and Commerce of the House of Representatives, the Committee on Health, Education, Labor, and Pensions of the Senate, appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry.

(2) <<NOTE: Federal Register, publication.>> Recommendations.--The Secretary shall publish in the Federal Register recommendations under paragraph (1), after negotiations with the regulated industry; shall present such recommendations to the congressional committees specified in such paragraph; shall hold a meeting at which the public may present its views on such recommendations; and shall provide for a period of 30 days for the public to provide written comments on such recommendations.

(b) Performance Report.--Beginning with fiscal year 2003, not later than 60 days after the end of each fiscal year during which fees are collected under part 2 of subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379g et seq.), the Secretary of Health and Human Services shall prepare and submit to the President, the Committee on Energy and Commerce of the House of Representatives, and the Committee on Health, Education, Labor, and Pensions of the Senate a report concerning the progress of the Food and Drug Administration in achieving the goals identified in the letters described in section 502(4) during such fiscal year and the future plans of the Food and Drug Administration for meeting the goals.

(c) Fiscal Report.--Beginning with fiscal year 2003, not later than 120 days after the end of each fiscal year during which fees are collected under the part described in subsection (b), the Secretary of Health and Human Services shall prepare and submit to the Committee on Energy and Commerce of the House of Representatives, and the Committee on Health, Education, Labor, and Pensions of the Senate, a report on the implementation of the authority for such fees during such fiscal year and the use, by the Food and Drug Administration, of the fees collected during such fiscal year for which the report is made.

SEC. 506. REPORTS OF POSTMARKETING STUDIES.

Section 506B of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356b) is amended by adding at the end the following subsections:

References

- *Coxibs and Cardiovascular Disease* by Garret A. Fitzgerald, M.D. New England Journal of Medicine, 21 October 2004
- *Failing the Public Health – Rofecoxib, Merck and the FDA* by Eric J. Topol, M.D. New England Journal of Medicine, 21 October 2004
- Who's Watching the Medicine Cabinet? By Scott Goldstein New Brunswick, 6 December 2004
- *Drug Firm Shares in Slump; Industry change may be necessary* by Brooke A. Masters. The Washington Post. 12 November 2004.
- *How drug-approval woes crept up on FDA; Critics charge conflict of interest in a system where phamaceutical giants fund the regulatory process* by Alexandra Marks. Christian Science Monitor. 26 November 2004.
- *Bureaucray and Representive Government* by William Niskanen. Chicago Ill.; Aldine-Atherton, 1971
- *Drugmakers Back user fee bill to speed FDA Drug approval* by Julie Roverner. Congressional Quarterly. 19 September 2000.
- *The Safety of Newly Approved Medicines: Do Recent Market Removals mean there is a problem?* By M.A. Friedman, J. Woodcock, M. Lumpkin, J.E. Shuren, A.E. Hass and L.J. Thompson. Journal of the American Medical Association, Vol. 281 (1999)
- *Pain Medicine;* Vioxx should have been withdrawn 4 years ago. Medical letter on the CDC and FDA. Atlanta. 5 December 1004.

- *Athritis drugmakers race to win over doctors.* Journal Record. Oklahoma City, Okla 11 November 1998.
- *Understanding NSAIDS:* from aspirin to COX-2; Gary A. Green; Clin Cornerstone 3(5): 50-59, 2001.
- *Cox*-2 inhibitors: A class act of just VIGORously promoted"; Samir Malhotra, N. Shafiz, P. Pandhi; Medscape General Medicine 6(1), 2004.
- *At what care level are cyclo*-oxygenase-2 inhibitors prescribed?; Montero Fernandez MD, Rodriguez, Alcala FJ, Valess Fernandez N, Lopez de Castro, F, Esteban, Tudela M, Cordero, Garcia B; Aten Primaria 30 October 2002.
- *Vioxx reduces night-time osteoarthritis pain better than celecoxib or acetaminophen;* European Leauge Against Rehumatism (EULAR) conference proceedings.
- *Will the promise of the COX*-II selective NSAIDS come to fruition?; Drug there Perspect 17(11); 6-10, 2001
- *Economic evaluation of celecoxib, a new cyclo*-oxygenase-2 specific inhibitor, in Switzer; JV Chancellor, E. Hunsche, E. de Cruz, F.P. Sarasin; Pharmacoeconomics 2001; 10 suppl `: 59-75
- *Osteoarthritis drug Celebrex less likely to cause increase blood pressure than Vioxx;* EULAR conference proceedings.

Online Readings

www.fda.gov

www.cder.gov

www.vioxx.com

www.merck.com