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IMPORTANT PRESCRIBING INFORMATION

April 2002

Dear Healthcare Professional:

Merck & Co., Inc., would like to bring to your attention recent changes to the current Prescribing Information and Patient Product Information for VIOXX® (rofecoxib tablets and oral suspension). VIOXX is a nonsteroidal anti-inflammatory drug (NSAID) that was approved by the United States Food and Drug Administration (FDA) in May 1999 for relief of the signs and symptoms of osteoarthritis (OA), the management of acute pain in adults, and the treatment of primary dysmenorrhea.

The Prescribing Information has been revised to reflect the results of the VIOXX Gastrointestinal Outcomes Research (VIGOR) Study and the FDA approval of VIOXX for the relief of the signs and symptoms of rheumatoid arthritis in adults. Excerpts of the changes to the Prescribing Information are provided below.

* * * * *

CLINICAL STUDIES

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.

Special Studies

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® (rofecoxib) compared to naproxen (see Table 1).

Table 1
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. 10½ 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 at approximately 10½ 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 2). This finding was largely due to a difference in the incidence of myocardial infarction between the groups. (See Table 3.) (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 2
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]	10½ 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 3
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*.

WARNINGS

Gastrointestinal (GI) Effects—Risk of GI Ulceration, Bleeding, and Perforation

[The standard NSAID warning of gastrointestinal effects is retained, with the following addition:]

Although the risk of GI toxicity is not completely eliminated with VIOXX® (rofecoxib), the results of the VIOXX GI outcomes research (VIGOR) study demonstrate that in patients treated with VIOXX, the risk of GI toxicity with VIOXX 50 mg once daily is significantly less than with naproxen 500 mg twice daily. (See CLINICAL STUDIES, *Special Studies, VIGOR*.)

PRECAUTIONS

Cardiovascular Effects

The information below should be taken into consideration and caution should be exercised when VIOXX® (rofecoxib) is used in patients with a medical history of ischemic heart disease.

In VIGOR, a study in 8076 patients (mean age 58; VIOXX n=4047, naproxen n=4029) with a median duration of exposure of 9 months, the risk of developing a serious cardiovascular thrombotic event was significantly higher in patients treated with VIOXX 50 mg once daily (n=45) as compared to patients treated with naproxen 500 mg twice daily (n=19). In VIGOR, mortality due to cardiovascular thrombotic events (7 vs 6, VIOXX vs naproxen, respectively) was similar between the treatment groups. (See CLINICAL STUDIES, *Special Studies, VIGOR, Other Safety Findings: Cardiovascular Safety.*) In a placebo-controlled database derived from 2 studies with a total of 2142 elderly patients (mean age 75; VIOXX n=1067, placebo n=1075) with a median duration of exposure of approximately 14 months, the number of patients with serious cardiovascular thrombotic events was 21 vs 35 for patients treated with VIOXX 25 mg once daily versus placebo, respectively. In these same 2 placebo-controlled studies, mortality due to cardiovascular thrombotic events was 8 vs 3 for VIOXX versus placebo, respectively. The significance of the cardiovascular findings from these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown. Prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators or placebo have not been performed.

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*; PRECAUTIONS, *Drug Interactions, Aspirin*.) Prospective, long-term studies on concomitant administration of VIOXX and aspirin evaluating cardiovascular outcomes have not been conducted.

ADVERSE REACTIONS

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%.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis

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

Management of Acute Pain and Treatment of Primary Dysmenorrhea

[The following statement has been added:]

Chronic use of VIOXX 50 mg daily is not recommended.

* * * * *

These and other changes are highlighted in the enclosed Prescribing Information and in the Patient Product Information, both of which are enclosed.

At Merck, we constantly evaluate data concerning our products. You can assist us in this regard by reporting all adverse experiences involving patients on VIOXX to the Merck National Service Center at 1-800-672-6372 or the FDA MedWatch program by phone at 1-800-FDA-1088, by FAX at 1-800-FDA-1078, or by mail at MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20857.

Please take the time to read the revised Prescribing Information and Patient Product Information for VIOXX, which are enclosed. Questions from healthcare professionals may be directed to the Merck National Service Center. Thank you very much for your time and attention.

Sincerely,

John Yates, MD
Vice President
Medical & Scientific Affairs
US Human Health

Enclosures: Prescribing Information for VIOXX® (rofecoxib)
Patient Product Information for VIOXX

20201077(1)-04/02-VIO

Printed in USA
Minimum 10% Recycled Paper