COX-2 INHIBITORS: LONG-AWAITED DRUGS IN THE PROCESS OF BEING TRIED AND TESTED

CeVEAS Information Pack no. 4
May 2002

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- *Clinical trials so far conducted on COX-2 inhibitors show, when compared to traditional NSAIDs, equal pain-relieving and anti-inflammatory efficacy (defined through qualitative measurements, both subjective and objective). On the other hand, the clinical efficacy of COX-2 inhibitors in treating acute non-articular pain (headache, toothache, etc.) has not been shown.*
- *Studies published demonstrate greater gastrointestinal tolerability of COX-2 inhibitors on the basis of both endoscopic and clinical results.*
- *The American Food and Drug Administration (FDA) has, however, reanalysed the data published, raising doubts about the overall safety profile of these drugs and, in particular, about adverse cardiovascular events.*
- *In this 'Information Pack' a study is made of the overall safety profile of COX-2 inhibitors, through the data available from the main clinical trials and from the FDA assessments. The tolerability of non-steroidal anti-inflammatory drugs according to the dose is also discussed, and it is emphasised how the effective dose changes according to the therapeutic objective (analgesic doses vs anti-inflammatory doses).*

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NSAIDs and COX-2 inhibitors: doses, risks and therapeutic objectives

✓ Do all NSAIDs have the same gastric perforation effect?

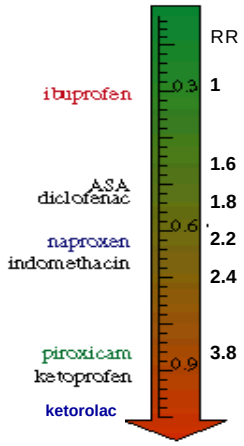
The results of observational studies (group, case-control studies) published in the '90s on the risks of NSAID-induced peptic ulcer or digestive haemorrhage[1] have shown that **NSAIDs have a different degree of gastric perforation**.
The **arrow shown on the right** displays increasing levels of gastric perforation on the part of ibuprofen, considered to be the safest NSAID from this point of view. Approximately 3 levels of gastric perforation may be considered:

- mild gastric perforation: ibuprofen
- intermediate gastric perforation: acetylsalicylic acid (ASA), diclofenac and naproxen
- severe gastric perforation: piroxicam and ketorolac.

The numbers beside the arrow indicate the relative risk (RR) of serious gastrointestinal complications associated with the use of individual NSAIDs, compared to ibuprofen, whose risk is considered equal to 1. The risk of ulcerous lesions associated with the use of **ketorolac** is over double that of diclofenac; the RR is not stated in the figure since the case-control study from which we obtained this result does not include ibuprofen[2]. **Ketoprofen** does not appear in the figure because the data on this medicine are not uniform: the high levels of gastric perforation shown by some studies could depend on the formulations available in some countries.

COX-2-specific inhibitors were developed starting from the assumption that this selective inhibition leads to a small risk of gastric perforation while maintaining the same anti-inflammatory activity.

Mild gastric perforation



Severe gastric perforation

Modified by: Therapeutics Letter, Jan/Feb 2001 http://www.ti.ubc.ca - Prescribing Practice review no. 2 Feb 1999 http://www.nps.org.au

✓ Is gastric perforation dose-dependent?

There is clear evidence that gastric perforation caused by NSAIDs is dose-dependent and, as dosage increases from medium-low to maximum doses, there is an approximate 3-fold increase in gastric perforation.
A case-control study on 1415 patients over 65 years of age in hospital for ulcerous disease being treated with NSAIDs (excluding ASA) at different dosages, showed a direct correlation between administered doses and appearance of peptic ulcers (see table on right). The risk is particularly high during the first month of therapy[3].

°In Italy piroxicam is available only in 20 mg doses.

Relative Risk of gastric or duodenal ulcer in relation to the use of standard doses in patients of > 65 years of age[3] on treatment with NSAIDs

NSAIDs	*Standard dose (mg)/day*	*Less than 2 standard doses*	*More than 2 standard doses*
ibuprofen	1200	2.2	3.3
indomethacin	50	3.1	6.0
naproxen	500	3.8	6.2
piroxicam°	20	6.3	-

✓ Can the therapeutic objective affect the dosage?

- Very often NSAIDs are prescribed for medical conditions (arthrosis, lumbar and sciatic pain, etc.) characterised by minimal or no inflammation, and are used as symptomatic drugs.
- **Osteoarthritis** (OA) is a chronic condition characterised by a degeneration of bone tissue with little inflammation. The treatment of **pain** is the main objective. Simple analgesics such as **paracetamol**, **COX-2 inhibitors** and NSAIDs at **low doses** are considered the treatment of choice.
- On the other hand, **rheumatoid arthritis** (RA), like other types of inflammatory arthritis, is characterised by a **major inflammatory element**. A reduction of the inflammation may be obtained by using specific antirheumatic drugs (for eg. gold salts, methotrexate, leflunomide, etc.), cortisones and NSAIDs.
- **Regardless of the drug used, anti-inflammatory doses are higher (indicatively double) compared to analgesic doses.**

Comparison between anti-inflammatory/antirheumatic doses and analgesic doses of various NSAIDs and COX-2 inhibitors

Drugs	*Analgesic dose*	*Analgesic effect*		*Antirheumatic dose*	*Antirheumatic effect*		*Max dose/day*
	mg	Start (hours)	Duration (hours)	mg	Start (days)	Duration (weeks)	mg
paracetamol	3000	0.5	4-6	*Does not have known antirheumatic effects*			4000
ibuprofen	1200	0.5	4-6	2400	Within 7	1-2	3200
naproxen	500	1	Up to 7	1000	Within 14	2-4	1250
diclofenac	100	-	-	150	-	-	200
indomethacin	50	0.5	4-6	100-150	7	1-2	200
piroxicam	20	1	48-72	20	7-12	2-3	20
celecoxib	200	3	-	400	-	-	400
rofecoxib	25	2-3	-	*Indication not recorded*			50

Modified by: Drug Facts & Comparisons® - July 2000

1 Henry D et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996;312:1563-6.
2 Traversa G et al. Gastroduodenal toxicity of different nonsteroidal antiinflammatory drugs. *Epidemiology* 1995;6:49-54.
3 Griffin MR et al. Nonsteroidal ani-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Annals Intern Med* 1991;114:257-263.

Gastric perforation caused by COX-2 inhibitors: CLASS and VIGOR studies

The pharmaceutical industries producing celecoxib and rofecoxib, after they were commercialised, promoted two RCTs with high sample numbers - the CLASS study and the VIGOR study respectively - in order to show a reduction in the incidence of complicated ulcers compared to non-selective NSAIDs. As drugs for comparison, the studies used maximum doses of ibuprofen (2400 mg), diclofenac (150 mg) and naproxen (1000 mg) and reported the results of a prolonged treatment (4.2 months for the CLASS study and 9 months for VIGOR).

Not included in the VIGOR study were patients being treated with low-dose ASA. This exclusion strongly limits the possibility of generalising the results of the study for this type of patient.

The incomplete results of these studies were published in the *JAMA*[1] and *N Engl J Med*[2] journals in 2000.

In the course of 2001, the FDA published on its website (www.fda.gov), the complete reviews of the CLASS and VIGOR studies[3-4], with a different interpretation of the safety profile of COX-2 inhibitors compared to traditional NSAIDs.
The FDA revealed that the version of the CLASS study published in *JAMA* only reported data relating to the adverse effects recorded in the first six months, while the study protocol had set out a longer-lasting treatment (12 and 15 months in the comparison with ibuprofen and diclofenac, respectively).

As regards the VIGOR study, the FDA emphasise the fact that serious adverse cardiovascular effects (especially myocardial infarction) associated with the use of rofecoxib were not reported by the authors.

CLASS study published in *JAMA*[1]
7968 patients randomised into three groups

PATIENTS: average age 60; 69% women
73% with osteoarthritis
average length of treatment: 4.2 months (max 6 months)
20% on treatment with low-dose ASA
(< 325 mg/day)

Celecoxib	Ibuprofen	Diclofenac
400 mg x 2	800 mg x 3	75 mg x 2
N=3987	N=1985	N=1996

VIGOR study published in the *N Engl J Med*[2]
8076 patients randomised into two groups

PATIENTS: average age 58; 80% women
100% rheumatoid arthritis
average length of treatment: 9 months (max 13 months)
patients treated with low-dose ASA
(< 325 mg/day) excluded

Rofecoxib	Naproxen
50 mg	500 mg x 2
N=4047	N=4029

Therapeutics Letter, Issue 41, Jan 2002 http://www.ti.ubc.ca

1 Silverstein FE et al. Gastrointestinal toxicity with celecoxib versus nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA*. 2000; 284:1247-1255.
2 Bombardier C et al, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med*. 2000; 343:1520-8.
3 US Food and Drug Administration. *Celebrex:* www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1.htm
4 US Food and Drug Administration. *Vioxx:* www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.doc

Gastrointestinal risks: data published in journals compared with complete FDA data

Adverse gastrointestinal outcomes in patients treated with CELECOXIB *vs* diclofenac or ibuprofen (data published in *JAMA*)

6-MONTH CLASS STUDY: *JAMA*					
Adverse outcomes	Incidence (% patients/year)[1]		Relative risk (CI)[2]	ARR%[3]	NNT[4]
	CELECOXIB *(1441 PAT/ YEAR)*	OTHER NSAD *(1384*			
Complicated ulcers	0.8	1.4	0.5 (0.3-1.1)	NS	NS
Complicated ulcers + symptomatic ulcers	2.1	3.5	0.6 (0.4-0.9)	1.4	69

Gastrointestinal adverse events in patients treated with CELECOXIB *vs* diclofenac or ibuprofen (data published by the FDA)

12-15-MONTH CLASS STUDY: FDA REPORT					
Incidence (% patients/year)[1]		Relative risk (CI)[2]	ARR%[3]	NNT[4]	
CELECOXIB *(2320 PAT/*	OTHER NSAD *(2203 PAT/*				
0.7	0.9	0.8 (0.4-1.4)	NS	NS	
1.8	2.8	0.7 (0.4-0.9)	1.0	105	

Adverse gastrointestinal events in patients treated with ROFECOXIB *vs* naproxen

9-MONTH VIGOR STUDY: *NEJM* AND FDA REPORT THE TWO ANALYSES ARE SIMILAR					
Adverse outcomes	Incidence (% patients/year)[1]		Relative risk (CI)[2]	ARR%[3]	NNT[4]
	ROFECOXIB *(2697 PAT/ YEAR)*	NAPROXEN *(2694 PAT/ YEAR)*			
Complicated ulcers	0.6	1.4	0.4 (0.2-0.8)	0.8	129
Complicated ulcers + symptomatic ulcers	2.1	4.5	0.5 (0.3-0.6)	2.4	42

Key to measurements used

NS = not statistically significant

[1] incidence = new cases for every 100 patients studied in one year

[2] relative risk (with COX-2 inhibitors instead of NSAIDs)

[3] absolute risk reduction (with COX-2 inhibitors instead of NSAIDs) for every 100 patients studied in one year

[4] number needed to treat (with COX-2 inhibitors instead of NSAIDs) in order to avoid an adverse event.

- ✓ The incidence of gastrointestinal events (complicated and non-complicated) is higher in patients who take naproxen at the maximum permitted doses, with respect to patients who take a 50 mg dose of ROFECOXIB. This difference is statistically significant.
- ✓ The incidence of complicated ulcers is higher in patients who take ibuprofen or diclofenac at the maximum permitted doses, with respect to patients who take CELECOXIB at the daily dose of 2 x 400 mg. This difference is reduced in the FDA analysis (that takes into account the whole period of the study - 12-15 months) compared to the conclusions published in *JAMA*, which are based on the first 6 months. The differences observed are not, however, statistically significant.
- ✓ Using a combined indicator (complicated ulcers + symptomatic ulcers), a "marginally" significant difference is found (p ~ 0.05) in favour of patients taking CELECOXIB. In this group, however, a smaller number of endoscopies was performed for confirming diagnosis. This difference is reduced in the FDA analysis (that takes into account the whole period of the study - 12-15 months) compared to the conclusions published in *JAMA*, which are based on the first 6 months.
- ✓ Celecoxib and rofecoxib cannot be compared to each other on the basis of the CLASS and VIGOR studies as the sample sizes studied are different.

Cardiovascular risks: data published by the FDA

Adverse cardiovascular outcomes in patients treated with CELECOXIB *vs* diclofenac or ibuprofen. The outcomes are expressed as incidence of cases for every 100 patients treated in one year.

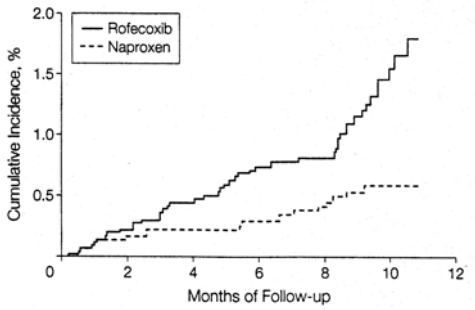
CLASS STUDY (FDA REPORT)		
Adverse outcomes	Incidence (% patients/year)	
	CELECOXIB *(2320 PAT/YEAR)*	OTHER NSAIDS *(2203 PAT/YEAR)*
Arrhythmia	0.6	0.3
Angina	1.3	1.0
Infarction	0.8	0.6
Withdrawal from trial due to adverse events	22.4	24.8
Serious adverse events	11.6	10.5
Cardiovascular mortality	0.5	0.4
Overall mortality	0.8	0.8

Since the differences between the two groups are not statistically significant, the reference statistical indices (relative risk, ARI, NNH) are not shown in the table.

✓ Adverse cardiovascular events in patients treated with ROFECOXIB and naproxen

VIGOR STUDY (FDA REPORT)					
Adverse events	Incidence (% patients/year)[1]		Relative risk (CI)[2]	ARI %[3]	NNH[4]
	ROFECOXIB *(2697 PAT/YEAR)*	NAPROXEN *(2694 PAT/YEAR)*			
Infarction	0.7	0.2	5.0 (1.7-14.3)	0.6	170
Stroke	0.4	0.3	1.2 (0.5-2.9)	NS	NS
Cardiovascular mortality	0.3	0.3	1.0 (0.4-2.9)	NS	NS
Infarction, stroke and cardiovascular mortality (combined)	1.3	0.7	1.9 (1.1 -3.4)	0.6	159
Overall serious adverse outcomes	14.5	12.0	1.2 (1.0-1.4)	2.5	40
Overall mortality	0.5	0.4	1.5 (0.8-2.8)	NS	NS

Cumulative incidence of cardiovascular events due to rofecoxib and naproxen. In the group treated with rofecoxib, an increase in events after the eighth month is particularly evident.



Key to the measurements used

NS = not statistically significant; *[1] incidence = new cases for every 100 patients studied in one year; [2] relative risk (with COX-2 inhibitors instead of NSAIDs); [3] Absolute risk increase (with COX-2 inhibitors instead of NSAIDs) for every 100 patients studied in one year; [4] number needed to harm (with COX-2 inhibitors instead of NSAIDs), in order to cause an adverse event.*

- ✓ The incidence of major cardiovascular events is higher in patients taking ROFECOXIB at a dose of 50 mg/day, with respect to patients taking naproxen at the maximum permitted doses. The differences observed are statistically significant and are particularly evident after the eighth month of use.
- ✓ The incidence of major cardiovascular events is higher in patients taking CELECOXIB at the daily dose of 2 x 400 mg, with respect to patients taking ibuprofen or diclofenac at the maximum permitted doses. These differences are not clinically or statistically significant.
- ✓ The data published by the FDA stress the major cardiovascular risks connected to the use of COX-2 inhibitors (in particular, rofecoxib). These risks were not adequately demonstrated by the authors of the VIGOR study.
- ✓ Celecoxib and rofecoxib cannot be compared with each other on the basis of the CLASS and VIGOR studies as the sample sizes studied are different.

COX-2 inhibitors and misleading advertising: FDA warnings

Between June 2000 and September 2001, the FDA sent a series of warning letters to the pharmaceutical companies producing rofecoxib and celecoxib regarding misleading promotional activities of the drugs. Below are reported some extracts of the letters dated 01/02/2001 and 17/9/2001 about the safety data of rofecoxib and celecoxib.

DEPARTMENT OF HEALTH & HUMAN

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Raymond V. Gilmartin
President and CEO
Merck & Co., Inc.
P.O. Box 1000, UG3BC-10
North Wales, PA 19454-109

RE: NDA 21-042
Vioxx (rofecoxib) tablets
MACMIS ID # 9456

WARNING LETTER

Dear Mr. Gilmartin:

This Warning Letter concerns Merck & Co. Inc.'s (Merck) promotional activities and materials for the marketing of Vioxx (rofecoxib) tablets. Specifically, we refer to promotional audio conferences given on behalf of Merck by Peter Holt, MD, a press release, and oral representations made by Merck sales representatives to promote Vioxx. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed your promotional activities and materials and has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and applicable regulations. See 21 U.S.C. §§ 331(a) and (b), 352(a), (f), and (n), and 355 (a).

You have engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular findings that were observed in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, and thus, misrepresents the safety profile for Vioxx. Specifically, your promotional campaign discounts the fact that in the VIGOR study, patients on Vioxx were observed to have a four to five fold increase in myocardial infarctions (MIs) compared to patients on the comparator non-steroidal anti-inflammatory drug (NSAID), Naprosyn (naproxen).

Although the exact reason for the increased rate of MIs observed in the Vioxx treatment group is unknown, your promotional campaign selectively presents the following hypothetical explanation for the observed increase in MIs. You assert that Vioxx does not increase the risk of MIs and that the VIGOR finding is consistent with naproxen's ability to block platelet aggregation like aspirin. That is a possible explanation, but you fail to disclose that your explanation is hypothetical, has not been demonstrated by substantial evidence, and that there is another reasonable explanation, that Vioxx may have pro-thrombotic properties.

*"… As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising and Communications has reviewed your **promotional activities** and materials and has concluded that **they are false, lacking in fair balance,** or otherwise **misleading in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations.**"*

COX-2 AND RISK OF MYOCARDIAL INFARCTION

"… in the VIGOR study, patients on [rofecoxib] were observed to have a four to five fold increase in myocardial infarctions (MIs) compared to patients on the comparator non-steroidal anti-inflammatory drug (NSAID), [naproxen]. Although the exact reason for the increased rate of MIs observed in the [rofecoxib] treatment group is unknown, your promotional campaign selectively presents the following hypothetical explanation for the observed increase in MIs. You assert that [rofecoxib] does not increase the risk of MIs and that the VIGOR finding is consistent with [naproxen's] ability to block platelet aggregation like aspirin. That is a possible explanation, but you fail to disclose that your explanation is hypothetical, has not been demonstrated by substantial evidence, and that there is another reasonable explanation, that [rofecoxib] may have pro-thrombotic properties".

COX-2 AND ORAL ANTICOAGULANTS

(...) "Your direct statement that [celecoxib] does not interact with [warfarin] directly contradicts the PI that clearly states, *"… in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving [celecoxib] concurrently with [warfarin]".*

In another letter, the FDA also admonishes the company producing rofecoxib, about the claim that COX-2 inhibitors "have the benefit of not having platelet aggregation and bleeding time". According to the FDA "this claim implies that [rofecoxib] is safer than other NSAIDs used in combination with warfarin. However, [rofecoxib] has not been studied in head-to-head trials prospectively designed to assess this specific *end-point*. Your superiority claim is therefore misleading".

COX-2 inhibitors and misleading advertising: FDA warnings (...continued)

COX-2 AND ADVERSE CARDIOVASCULAR EVENTS

(...)"Your suggestion that COX-2 inhibitors, including [rofecoxib], have an overall safety profile that is superior to other NSAIDs is misleading because such an advantage has not been demonstrated. In fact, in the VIGOR study, the incidence of serious adverse events was higher in the [rofecoxib] treatment group than in the naproxen treatment group (9.3% and 7.8% for [rofecoxib] and naproxen, respectively). The results of safety analyses that were pre-specified in the protocol for the VIGOR trial, such as CHF-related adverse events and discontinuations due to edema-related adverse events, hepatic-related adverse events, hypertension-related adverse events, and renal-related adverse events, were all numerically higher (in some cases statistically significantly higher) in the [rofecoxib] treatment group than in the naproxen treatment group".

Other considerations

COX-2 and ELDERLY PATIENTS

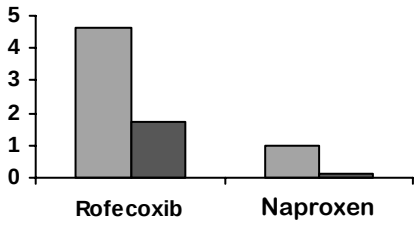
The data published in the CLASS and VIGOR studies and the FDA reports, do not allow a higher efficacy or safety of COX-2 inhibitors to be established in specific age groups (no analyses have been carried out for subgroups). In fact, only the age *of the participants (60 and 58 years of age, respectively)* has been specified.

COX-2 and ASA at anti-aggregant doses

Greater gastrointestinal tolerability of COX-2 inhibitors compared to non-selective NSAIDs was not shown in patients who must take low-dose aspirin as an anti-aggregant. In particular, the CLASS study highlights the fact that there are no differences in tolerability in this subgroup of patients.

COX-2 and HYPERTENSION

In the VIGOR study, there was an average increase in blood pressure among patients treated with rofecoxib that was higher than that of patients treated with naproxen[1].



Variations in average values (mm Hg) of systolic and diastolic blood pressure during the VIGOR study.

[1] Mukherjee D et al. *JAMA* 2001;286:954-959

SUMMARY

- ✓ *The versions of the CLASS and VIGOR studies published in the international journals (New England Journal of Medicine and JAMA) showed greater gastrointestinal tolerability towards COX-2 inhibitors when compared to traditional NSAIDs at full dosage (ibuprofen 2400 mg, diclofenac 150 mg, naproxen 1000 mg).*
- ✓ *After having reanalysed all the data in the CLASS and VIGOR studies, the FDA showed a less favourable tolerability profile compared to that published in the scientific journals and highlighted an inaccurate promotional activity, which tended to minimise certain serious adverse events that emerged during the clinical trials.*
- ✓ *On the basis of what the FDA published, rofecoxib is associated with a significant increase in the incidence of the risk of serious adverse cardiovascular events compared to naproxen.*
- ✓ *It is therefore necessary to be very careful in prescribing these drugs on a long-term basis to patients at high cardiovascular risk.*
- ✓ *Celecoxib and rofecoxib cannot be compared with each other on the basis of the CLASS and VIGOR studies as the sample sizes studied are different.*

The full version of the FDA's Warning Letters are available at the following web addresses:

Rofecoxib: http://www.fda.gov/foi/warning_letters/g1751d.pdf Celecoxib: http://www.fda.gov/foi/warning_letters/m5097n.pdf

Joint prescription of proton pump inhibitors and COX-2 inhibitors: what do the results tell us?

Modena 2001

Analysis of National Health Service prescriptions

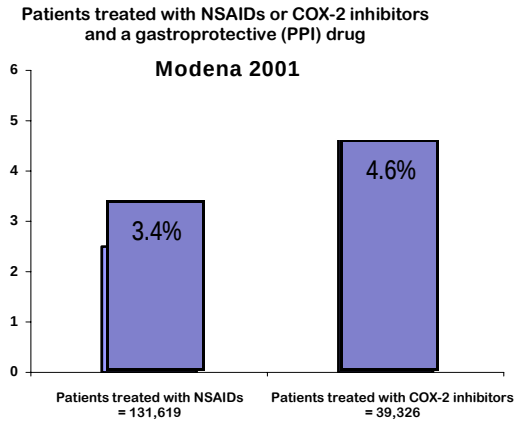
The table on the right shows, for each drug subgroup, the number of DDD (daily defined doses) per 1000 inhabitants per day prescribed by the NHS (through GPs and Independent Paediatricians at the Modena NHS Trust Hospital) and the difference in relation to the previous year.
One year after its commercialization (2000), a substantial increase was recorded in the prescription of COX-2 inhibitors (+233%). Furthermore, taking into consideration the low gastric perforation effects of these drugs, a reduction in the use of gastric protection was expected (note CUF 1), but instead, it increased by 60%.

	DDD x 1000 inhabitants/day		
DRUGS	2000	2001	DIFF.%
NSAIDs	8.8	9.9	+12
Ketorolac	0.5	0.5	0
Oxicam-derivates	2.9	2.6	-10
COX-2 inhibitors	1.5	5.0	+233
Pump inhibitors	6.2	9.9	+60
Anti-H_2	2.7	2.6	-4
Misoprostol	0.4	0.3	-25
Total prescriptions (all drugs)	*541.6*	*633.0*	*+17*

In order to assess the possible joint prescription with proton pump inhibitors (PPI), we carried out an ad hoc analysis cross-referencing the database of prescriptions with the personal details of the patients. Patients who had been prescribed an NSAID and/or a COX-2 inhibitor in association with a pump inhibitor as a gastroprotective drug on the same day were identified.

As can be seen in the figure on the right, the result of the data is that the percentage of association of COX-2 inhibitors and proton pump inhibitors is higher than the percentage of association of NSAIDs and proton pump inhibitors.

These results are confirmed even when the patients who were given at least one prescription for proton pump inhibitors during the previous six months are excluded. Thus, the aim was to exclude patients treated with a proton pump inhibitor regardless of an anti-inflammatory drug being taken.



ITALY 2001

ACTIVE DRUG	2001 COSTS IN MILLIONS OF EUROS	% OF TOTAL COSTS	LIST 2000	LIST 2001
Celecoxib	134	1.11	101	13
Rofecoxib	99	0.82	78	25
Naproxene	8	0.07	231	247
Diclofenac	44	0.37	81	92
Total NHS expenses	*12,146*			

The national report on the consumption of drugs outside the hospital (both public and private) environment presented by OsMED (Italian National Drug Use Monitoring Center) states that "*COX-2 inhibitors are among the substances that have contributed the most to the increase in NHS costs*".
In particular, it stresses that **celecoxib** has gone from 101st to 13th place and **rofecoxib** from 78th to 25th place in the list of substances in terms of costs.

The report is available on the website
www.sanita.it/osmed/rapporti.asp