COX-2 INHIBITORS AND MYOCARDIAL INFARCTION

A CLASS EFFECT

THE RECENT PAST

- CeVEAS Information Pack no. 4 (2002) reported the initial doubts about the negative effect of COX-2 inhibitors on the cardiovascular system with respect to traditional NSAIDs.
- Surprising was the fact that after the results of the VIGOR study (2000), the regulatory agencies did not request pharmaceutical companies for studies designed with the objective of clarifying those doubts.
- It was only in the spring of 2004 that the EMEA (European Medicines Evaluation Agency) re-assessed the safety profile of COX-2 inhibitors on the basis of a request made by France in 2002. From that moment on, the drug information leaflets of all COX-2 inhibitors had to contain a warning relative to cardiovascular safety, and in particular, to the risk of myocardial infarction.

THE STORY SO FAR

- On **30th September 2004**, Merck Sharp & Dohme voluntarily withdrew rofecoxib from the world market.[1]
- On **16th December 2004**, the American National Cancer Institute stopped the APC study with celecoxib.
- On **17th February 2005**, the EMEA introduced some limitations to the use of COX-2 inhibitors.
- On **18th February 2005**, members of the FDA Advisory Panel approved carrying on with sales of celecoxib and valdecoxib and the possible re-introduction of rofecoxib.
- On **7th April 2005**, the FDA and EMEA asked the pharmaceutical company to voluntarily withdraw valdecoxib from the market because of an unfavourable risk/benefit ratio.

This information pack presents the main data produced in the last two years on the cardiovascular safety of COX-2 inhibitors.

SUBJECTS COVERED

Rofecoxib: the withdrawal of a best-seller

- ✓ A 25 mg dose of rofecoxib increases the frequency of major cardiovascular (CV) events with respect to placebo.
- ✓ It is not clear whether the risk appears early or whether it depends on the duration of the treatment.
- ✓ This result led to the withdrawal of the drug from the market by the pharmaceutical company.

THE APPROVe STUDY AND THE WITHDRAWAL OF ROFECOXIB

On 30th September 2004, following an interim analysis of the APPROVe[2] study, which demonstrated a significant increase in myocardial infarction with rofecoxib compared to placebo, **M**erck, **S**harp & **D**ohme immediately withdrew rofecoxib from the market and suspended all ongoing experimental studies.[1]

Main CHARACTERISTICS of the APPROVe study

Comparison of treatments and no. of patients	• **Rofecoxib 25 mg/day** • **Placebo**	• **1287 pat.** • **1299 pat.**
Objective of the study	• prevention of recurrence of polyps in patients with a history of colorectal adenomas	
Duration	• scheduled duration: 3 years (terminated two months before end)	
Patients studied (total = 2586)	• average age 59 years; 62% male • 17% in therapy with low-dose aspirin	
Patients excluded	• with familial adenamatous polyposis, previous stroke or TIA, angina, congestive heart failure, myocardial infarction, previous coronary angioplasty or previous coronary-artery bypass grafting	

Main RESULTS of the APPROVe study

	Rofecoxib (1287 patients)	**Placebo (1299 patients)**
Main outcome of CV safety	No. of patients (%)	
Serious CV thrombotic events in 2.5 years*	46 ‡ (3.6%)	26 ‡ (2.0%)

**Sum of: fatal and non-fatal MI, unstable angina, sudden death, fatal and non-fatal ischemic stroke, TIA, peripheral venous and arterial thrombotic events.*
‡ *statistically significant difference*

WHAT WE KNEW OR COULD HAVE KNOWN

- ▶ In 2000 the **VIGOR**[5,6] study (see CeVEAS Information Pack no. 4) highlighted a 5-fold increase in the risk of infarction in patients treated with rofecoxib as compared to those treated with naproxen (~ 0.4% *vs* ~ 0.1%).
- ▶ A 2004 systematic review[7] (Juni P et al.) pointed out that the incidence of **myocardial infarctions more than doubled** in patients who took rofecoxib rather than non-selective NSAIDs.
- ▶ The authors emphasise that if a meta-analysis had been performed using published data, it would have shown a **statistically significant risk of infarction for rofecoxib as long ago as at the end of 2000.**

- ▶ Rofecoxib causes around a two-fold increase in the frequency of cardiovascular events as compared to placebo. In particular, treating 1000 patients who are at low cardiovascular risk for one year would result in an average of 8 additional serious cardiovascular thrombotic events.
- ▶ Therefore, the protracted use of rofecoxib is associated with a greater CV risk, more than 15% if projected to 10 years.[3] For such a risk, the cardiovascular prevention guidelines recommend using aspirin at low doses.

DOES CV RISK DEPEND ON DURATION?
The data available are controversial

- ▶ In the APPROVe[2] study, thrombotic risk becomes statistically significant after only 18 months, while the increase in cases of heart failure and pulmonary oedema are already in evidence in the first few months.
- ▶ The Juni systematic review[7] shows that there is a CV risk of rofecoxib in both short- and long-term studies and that it is not dose-dependent.
- ▶ Two factors that seem relevant to a further increase in risk are the age and basic cardiovascular conditions of the patients treated.[8,9]

An RCT on celecoxib also discontinued

- ✓ The randomised APC study was stopped early because of an excessive number of cardiovascular events with celecoxib compared to placebo.
- ✓ This increase was found to be dose-dependent.

On 16th December 2004, the American National Cancer Institute[10] stopped the randomised APC study[11] due to an excess of fatal and non-fatal cardiovascular events in patients treated with celecoxib as compared to those treated with placebo.

Main CHARACTERISTICS of the APC study

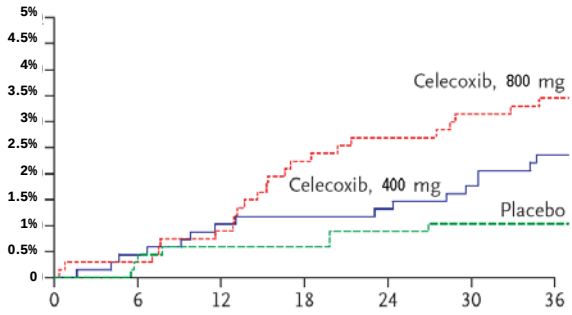
Comparison of treatments and no. of patients	• **Celecoxib 400 mg/day** • **Celecoxib 800 mg/day** • **Placebo**	• **685 pat.** • **671 pat.** • **679 pat.**
Objective of the study	• prevention of recurrence of polyps in patients with a history of colorectal adenomas	
Duration	• scheduled duration: 3 years (terminated two months before end)	
Patients studied (total = 2035)	• average age 60 years; 68% male • 30% in therapy with low-dose aspirin	

WHAT WE ALREADY KNEW: PUBLISHED AND UNPUBLISHED DATA

- Since the CLASS study[5,13] (see CeVEAS Information Pack no. 4), which did not highlight the differences in cardiovascular safety between celecoxib and ibuprofen or diclofenac, 52 randomised clinical trials (RCTs) have been published of which 12 had a sample size of more than 450 patients and a minimum duration of 6 weeks (2 of these re-elaborate data from the CLASS study).
- In none of these studies has the main indicator evaluated been major cardiovascular outcomes.
- An RCT on 13,000 patients followed for 12 weeks (called SUCCESS–I and never published in detail in a scientific journal)[14] evaluated the efficacy and the safety of celecoxib (200–400 mg/day) with respect to diclofenac (100 mg/day) or naproxen (1000 mg/day). The data available does not allow an adequate interpretation of the results.

Main RESULTS of the APC study

INCIDENCE OF FATAL AND NON-FATAL CARDIOVASCULAR EVENTS*



**death from cardiovascular causes, non-fatal MI, stroke or heart failure*

The analysis of data shows an increase of dose-dependent cardiovascular risk[12] with celecoxib.

Treating 1000 patients for one year results in an average of:

- 3.4 CV events with placebo
- 7.8 CV events with celecoxib 400 mg/day (**4.4 more than placebo**, i.e a 2.3-fold increase)
- 11.4 CV events with celecoxib 800 mg/day (**8 more than placebo**, i.e a 3.4-fold increase)

WHEN RESULTS ARE NOT PUBLISHED…

Missing publications in scientific journals of studies with negative clinical outcomes generate so-called publication *bias* (systematic error). In other words, one can have a distorted view of the efficacy and/or safety of a health intervention because positive results are easier to publish than negative ones.[15]

Celecoxib and rofecoxib … what can observational studies tell us?

- ✓ Observational studies on large sample sizes have shown the existence of cardiovascular risks associated with the use of rofecoxib and have excluded such risks for celecoxib.
- ✓ These results, refuted by one RCT, should anyway be interpreted with caution due to the risk of systematic errors and confounding factors.

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A "comparison" … unequal though it is

	OBSERVATIONAL STUDIES	*RANDOMISED CLINICAL TRIALS (RCT)*
CHARACTERISTICS	▶ Evaluate the frequency of clinical outcomes in users of COX-2 inhibitors or other NSAIDs[16-20] in comparison with non-users. ▶ Treatments are not allocated experimentally, but are "observed" during normal clinical practice.	▶ COX-2 inhibitors are compared with another NSAID or with placebo and allocation to each group is carried out in a casual manner (randomised).
ADVANTAGES	▶ The possibility to analyse large sample sizes (in the order of hundreds of thousands of individuals) and to enable data gathering of rare side effects or to put forward hypotheses on unknown clinical effects.	▶ Randomisation increases the probability of groups that are being compared to each other having similar characteristics and prognostic factors. Therefore, possible differences observed between the groups can almost certainly be attributed to the treatment. ▶ RCTs are thus the most trustworthy instrument to assess the efficacy and, if the sample size studied is sufficient, the safety of a medicine.
DISADVANTAGES	▶ One cannot be certain that patients undergoing therapy with comparative drugs - specifically, celecoxib, rofecoxib or other NSAIDs - have similar characteristics.	▶ A randomised study that is long-term and conducted on a large sample size is expensive and imposes selection criteria on patients that can limit the transferibility of the results to clinical practice. Moreover, it is complex from an organisational point of view.

CELECOXIB: THE RISKS EXIST NOTWITHSTANDING THE RESULTS OF OBSERVATIONAL STUDIES

- ▶ Some observational studies with large sample sizes (from 50,000 to about 1,400,000 individuals studied)[16-20] have suggested that the risk of cardiovascular events with celecoxib is small with respect to rofecoxib, and similar to the risk faced by those who do not use NSAIDs or use non-selective NSAIDs.
- ▶ In December 2004, the randomised APC study[11] (see pg. 3) was discontinued, disproving the results of observational studies conducted in the past.
- ▶ This again demonstrates that the results of observational studies cannot be considered conclusive.

What is known about the other COX-2 inhibitors available in Italy?

- ✓ No detailed randomised studies that allow the assessment of cardiovascular safety have been published for etoricoxib. However, a greater risk of complications related to hypertension have been demonstrated.
- ✓ Pare/Valdecoxib is associated with an increase in major cardiovascular events (when it is used in acute cases) and with severe skin reactions.

Pare-Valdecoxib

- **2** RCTs carried out in patients undergoing coronary-artery bypass grafting have confirmed an **increase** in **cardiovascular risk** with both **valdecoxib** and **parecoxib** (prodrug of valdecoxib that can be administered intravenously) used for **brief periods** in the treatment of post-operative pain (10-14 days).[21,22]
- The first study[21] (462 patients with an average age of 61 years) highlighted a significant doubling of serious adverse outcomes (19.0% *vs* 9.9%) in patients who took COX-2 inhibitors instead of the standard analgesic treatment with morphine.
- In the second study[22] (1671 patients with an average age of 62 years) the cardiovascular events were significantly more frequent in the group treated with pare/valdecoxib (2.0%) than in the group treated with placebo (0.5%).
- A metanalysis[23] of the two studies shows that the risk of cardiovascular events associated with valdecoxib is three times higher than that with placebo (RR=3.08 IC 95% 1.20—7.87).

BEWARE OF ADVERSE SKIN REACTIONS

In 2002, the EMEA issued a warning on the elevated number of **severe reactions** of **hypersensitivity** (anaphylaxis and angioedema) and of **skin** (among which are Stevens Johnson Syndrome and toxic epidermal necrolysis) associated with the use of **parecoxib and valdecoxib** in the first 2 weeks of treatment itself. Since then, 87 cases of Stevens Johnson Syndrome have been indicated, including 36 recoveries and 4 deaths.[24-26]

On the basis of these considerations, the FDA and the EMEA requested Pfizer to voluntarily suspend sales of **valdecoxib**.

Etoricoxib

- 15 RCTs have been published on the efficacy and safety of etoricoxib, of which only 7 involve more than 450 patients and last a maximum of 12 weeks. CV safety data are limited to surrogate clinical outcomes (for eg. peripheral oedemas) for which no differences have been shown compared to traditional NSAIDs.
- Notwithstanding this, etoricoxib has become the most prescribed COX-2 inhibitor ever (see pg. 8), overtaking even rofecoxib — produced by the same pharmaceutical company — right from its first month on the market.

Mors tua vita mea

- **Interactions**: it is indicated (in the Product Characteristics Summary as well)[27] that the concomitant use of etoricoxib and oral contraceptives or substitutive hormonal therapy results in an **up to 60% increase of plasma concentrations of estrogens** and a consequent increase in the incidence of adverse events (for eg. thromboembolic events in women at risk).

UNPUBLISHED DATA AND ONGOING STUDIES

- EDGE, a randomised study with a large sample size (7111 arthrosis patients), compared etoricoxib (90 mg/day, 3593 patients) with diclofenac (3x50 mg/day, 3518 patients) for an average of 9 months. The analysis of the data (available only on the FDA website[28]) shows that the number of **myocardial infarctions is greater** with etoricoxib than with diclofenac, even though it is not statistically significant (0.65 *vs* 0.42 events respectively for every 100 patients treated for one year), and that dropouts due to adverse effects related to hypertension were significantly higher in etoricoxib patients (2.3% *vs* 0.7%).
- An ongoing RCT, involving 23,000 patients and which is due to last 1.5 years, compares the **cardiovascular risks** of etoricoxib (60 and 90 mg) and diclofenac (150 mg) in patients with osteoarthritis and rheumatoid arthritis.

Lumiracoxib: the COX-2 inhibitor yet to make an appearance in Italy

- ✓ Notwithstanding its large sample size, the TARGET study was designed to assess the gastrointestinal safety and not the cardiovascular safety of lumiracoxib.
- ✓ Even though it was at the limit of statistical significance, the study pointed out double the incidence of infarctions in patients treated with lumiracoxib rather than with naproxen.

TARGET: a study with a large sample size but ...

- Lumiracoxib, not available yet in Italy, was the subject of the **TARGET**[29] study, which assessed the gastrointestinal safety (main objective) and cardiovascular safety (secondary objective) after one year of treatment with 400 mg of lumiracoxib a day (from two to four times the standard dose for the treatment of osteoarthritis), and compared this dose with ibuprofen and naproxen in **two different substudies**.
- The sample size was, however, specifically defined so that differences in the frequency of gastroduodenal ulcers in the two combined substudies could be observed.
- Therefore, this RCT, carried out on a low CV risk population (only 10-13% is at high CV risk) for a limited duration of 1 year, **did not have a large enough sample size** ("statistical power") to show a possible difference in cardiovascular risk between **lumiracoxib and naproxen**.

Main CHARACTERISTICS of the TARGET study

Comparison of treatments and no. of patients	• **lumiracoxib 400 mg/day** • **ibuprofen 800 mgx3/day** • **naproxen 500 mgx2/day**	• **9117 pat.** • **4397 pat.** • **4730 pat.**
Main objective	• assess gastrointestinal safety (complicated ulcers)	
Cardiovascular outcomes	• non-fatal MI + non-fatal stroke + cardiovascular death (composite clinical events)	
Duration	• 52 weeks	
Patients included (tot= 18.325)	• average age 63 years; 76% female • 24% in therapy with low-dose aspirin	
Patients excluded	• with previous MI, stroke, undergoing coronary-artery bypass grafting or with congestive heart failure	

Main RESULTS of the TARGET study

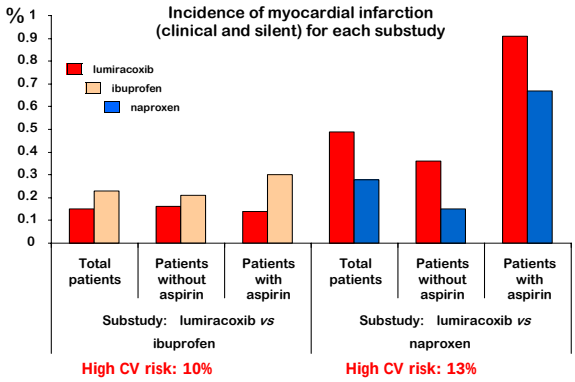


Figure 1. Frequency of infarctions at **one year** for each of the two substudies, also considering the possible use of low-dose aspirin.

Some doubts on CV safety still remain

- The patients in the two substudies had a different baseline CV risk (10 *vs* 13%, see Figure 1) thus making the comparison of the different drugs more difficult.[30]
- The differences in pressure variations favour lumiracoxib with respect to other NSAIDs (-1.7 mm Hg in systolic blood pressure, -0.4 mm Hg in diastolic blood pressure).
- The differences observed in the major cardiovascular outcomes are not statistically significant both on distinguishing between the two substudies (as in the above graph) and on combining the results. It is a good idea to repeat here that the study was not designed to establish the possible differences in cardiovascular safety.[30]
- Despite not reaching statistical significance, the incidence of infarction in patients treated with lumiracoxib is about double with respect to those treated with naproxen (0.49% *vs* 0.28%).

What do the prescription data suggest?

Information recorded on 30th September 2004

	Rofecoxib	Celecoxib	Etoricoxib	Valdecoxib	Parecoxib
Osteoarthritis	✓	✓	✓	✓	
Rheumatoid arthritis	✓	✓	✓	✓	
Acute gouty arthritis			✓		
Acute pain	✓				
Primary dysmenorrhea	✓			✓	
Post-operative pain					✓

Beware of CV risk factors

ASL Modena: January - September 2004. From the analysis of data of territorial prescriptions during January—September 2004, COX-2 inhibitors were found to be more prescribed in patients of age ≥ 75 years. The prescription of low-dose aspirin was higher in this age group.

Figure 1. Prescriptions of non-selective NSAIDs and COX-2 inhibitors (DDDx1000 inhab./day) per age group

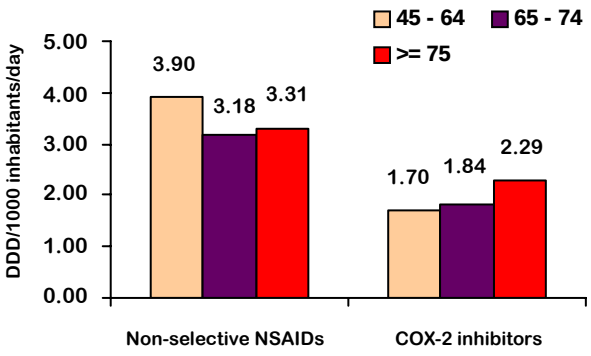
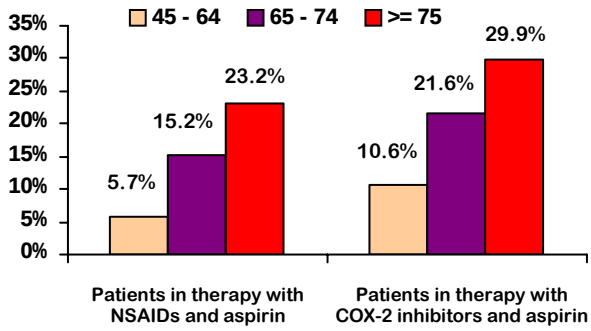


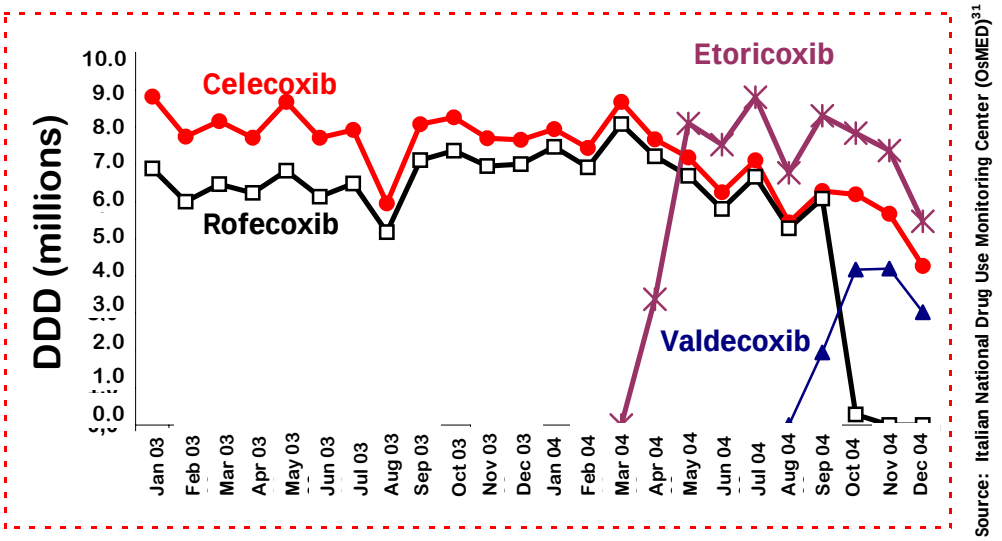
Figure 2. Patients treated per age group with non-selective NSAIDs or COX-2 inhibitors in association with low-dose aspirin



= 11,380 = 4,019

The commercial success of COX-2 inhibitors in Italy (2003—2004)

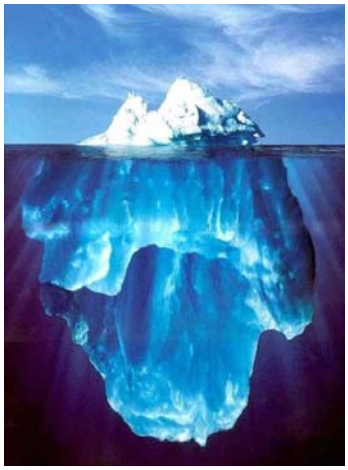
- The prescription of COX-2 inhibitors continues to rise (+26% in the last year). A growth has been observed in the consumption of the new drugs, and in particular of etoricoxib, which from May 2004, became "the favourite COX-2 inhibitor of the Italians".
- Since October 2004 (after the withdrawal of rofecoxib), the prescriptions for all COX-2 inhibitors have gone down in number.



To recap ...
use COX-2 inhibitors with caution

The submerged evidence

- A complete assessment of existing data carried out as early as at the end of 2000 would have allowed confirmation of the cardiovascular risks of rofecoxib as highlighted in the VIGOR study.[20]
- Considering the great use of these drugs, it is estimated that in the 5 years of their commercialization in the United States alone, around 100,000 individuals may have had an infarction attributable to the use of rofecoxib.[29]



Hesitation by the EMEA and the FDA

- It was only after the withdrawal of rofecoxib that the European and American regulatory agencies — the EMEA and FDA — decided to initiate reviews in order to assess the extent of cardiovascular risks of COX-2 inhibitors.
- The EMEA decided to contraindicate all COX-2 inhibitors in patients with ischaemic cardiopathy or previous stroke, and for etoricoxib, the contraindication was also extended to patients with non-controlled hypertension. The prescribing doctor would have to pay special attention to the presence of other cardiovascular risk factors such as hyperlipidaemia, diabetes, smoking habits and peripheral vasculopathy. Given the association between CV risk and exposure to COX-2 inhibitors, the EMEA recommends using a lower dose and limiting the duration of treatments. This decision goes against the reasons that have supported the registration of COX-2 inhibitor treatments (i.e better gastric tolerability in long-term treatments).
- After having re-assessed the risk-benefit profile of the whole class, an FDA Panel gave its approval to carry on with sales of celecoxib and valdecoxib and for the possible re-introduction of rofecoxib.

BENEFITS

- All COX-2 inhibitors have demonstrated an efficacy in alleviating pain comparable to that of non-selective NSAIDs in non-inferiority studies.
- A reduction in complicated gastro-duodenal ulcers compared to non-selective NSAIDs was shown in RCTs with at least 1000 patients only for rofecoxib and lumiracoxib (in the case of the latter, only in patients without low-dose aspirin).
- The data on celecoxib are controversial because the study with a large sample size, CLASS[5], has important methodological limitations.

RISKS

- The demonstration of an increase in cardiovascular risk with different COX-2 inhibitors suggests a possible "class effect".
- These risks are present, in particular, for rofecoxib, celecoxib and pare/valdecoxib, and their absence is uncertain for lumiracoxib.
- Etoricoxib increases the adverse outcomes related to hypertension.
- Pare/Valdecoxib can also cause severe skin reactions and hypersensitivity.

Authors:
Annalisa Campomori,
Oreste Capelli,
Giulio Formoso,
Anna Maria Marata,
Nicola Magrini
CeVEAS, Modena

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The decisions of the Regulatory Agencies in April 2005

IN EUROPE[32,33,35]

- **All COX-2 inhibitors are contraindicated** in patients with ischaemic cardiopathy or established cerebrovascular disease and congestive heart failure (Class NYHA II-IV).¶
- **Particular attention** must be paid while prescribing to patients with cardiovascular risk factors and with peripheral vasculopathy.
- **Moreover**:

ROFECOXIB
- **After** withdrawal from the market, it has still not been evaluated.

ETORICOXIB
- **It is contraindicated** in people with non-controlled hypertension.

PARE/VALDECOXIB
- **It must not be used** in the treatment of post-operative pain consequent to coronary-artery bypass grafting.

LUMIRACOXIB
- *The drug is awaiting registration (by Mutual Recognition Procedure) in all countries belonging to the European Community.*

¶ Patients with these conditions who take COX-2 inhibitors must be given alternative treatments.

On 7th April, following a request by the **EMEA**, Pfizer suspended the sale of **valdecoxib** in Europe.

IN THE USA[34]

On 16th, 17th and 18th February 2005, the FDA had a public meeting on COX-2 inhibitors with the members of the Advisory Panel in order to re-assess the safety profile of these drugs.

A majority of the Panel was in favour of carrying on with sales of celecoxib and valdecoxib and the re-introduction of rofecoxib despite differences in the consensus (see table).

	👍	👎
ROFECOXIB	17	15
CELECOXIB	31	1
VALDECOXIB*	17	13
*2 abstentions		

The Panel recommended the insertion of a special warning (**BLACK BOX**) concerning cardiovascular risks in the Product Characteristics Summary of all COX-2 inhibitors on sale in the USA. The FDA will have to express a definite opinion on the basis of these recommendations.

On 7th April, Pfizer voluntarily withdrew **valdecoxib** from the US market too as per a request by the **FDA**.