POSITION STATEMENT

Considerations for the safe prescribing and use of COX-2-specific inhibitors

The Australian COX-2-Specific Inhibitor (CSI) Prescribing Group*

ABSTRACT

The majority of the "Australian COX-2-Specific Inhibitor (CSI) Prescribing Group" endorse the following points:

- CSIs are equivalent to non-steroidal anti-inflammatory drugs (NSAIDs) as anti-inflammatory agents.
- CSIs and NSAIDs modify symptoms but do not alter the course of musculoskeletal disease.
- CSIs do not eliminate the occurrence of ulcers or their serious complications, but are associated with considerably fewer peptic ulcers, slightly fewer upper GI symptoms and, according to published reports, fewer serious upper GI complications, notably bleeding, than NSAIDs.
- CSIs and NSAIDs have similar effects on renal function and blood pressure.
- Whether any CSI poses a risk to cardiovascular safety remains subject to debate.
- Comorbidities and coprescribed drugs must be considered before initiating CSI (or NSAID) therapy.
- Patients prescribed CSIs (or NSAIDs) should be reviewed within the first few weeks of therapy to assess effectiveness, identify adverse effects and determine the need for ongoing therapy

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THE AVAILABILITY of the COX-2-specific inhibitor (CSI) class of anti-inflammatory drugs, namely celecoxib and rofecoxib, has raised a number of questions. These include:

- to what extent do the CSIs reduce serious gastrointestinal (GI) toxicity?
- what is their place in patients with peptic ulcers or cardiovascular disease, or with risk factors for these conditions?
- do they still have a place in patients who need low-dose aspirin for its antiplatelet effect?
- are they safer than non-steroidal anti-inflammatory drugs (NSAIDs) in patients with hypertension and renal impairment?
- are there significant issues in patients with other diseases or taking other drugs?
- is the benefit/toxicity profile the same for both celecoxib and rofecoxib?

As every clinician considering the use of a CSI or an NSAID must somehow take such questions into account, it seemed appropriate that physicians and general practitioners with experience in the use of these drugs offer their own assessment of the issues and the approach they consider reasonable in different clinical situations.

Therefore, a working group was formed with the following aims:

- to survey published data from therapeutic studies to determine the strength of evidence bearing on GI safety, cardiovascular safety, renal and blood pressure effects, co-prescribing and comorbidity effects, and allergy and intraclass differences; and
- to generate from that survey considerations for safe CSI use.

The working group was constituted primarily by the rheumatologists on the medical advisory boards of Pharmacia/Pfizer and Merck, Sharp & Dohme, the two pharmaceutical companies responsible for the development and marketing of celecoxib and rofecoxib, respectively. Meloxicam was not considered, as it was not marketed at the time the working group met. A number of experts from general practice, clinical epidemiology, gastroenterology, cardiology, nephrology, and individuals associated with relevant bodies including the National Prescribing Service, the Arthritis Foundation of Australia (AFA), the Australian Rheumatology Association (ARA) and the medical departments of the pharmaceutical companies, were invited to join. Financial support for meetings of the working group was provided by Pharmacia/Pfizer, Merck Sharp & Dohme, the AFA and the ARA; these funds were used for travel and meeting expenses. No remuneration was paid to members of the working group.

We acknowledged that the exercise could only have value if undertaken independently of any but scientific influence (ie, that working group members should not continue to act in the capacity of an advisory group to industry, but rather broadly in the best interest of all stakeholders — patients, doctors, the pharmaceutical industry and the public. The working party agreed that it must be autonomous with respect to its terms of reference, and that its conclusions and recommendations should be based on a fair assessment of the literature published up to the end of May 2001 and pertinent sections of the United States Food and Drug Administration (FDA) website, accessible in the public domain. The cost of CSIs was not considered, as there is little pertinent "cost-effectiveness" literature in the public

For editorial comment, see page 304; see also page 332

** Members of the working group are listed in a Box at the end of this article.*

The Australian COX-2-Specific Inhibitor (CSI) Prescribing Group
C/- Clinical Pharmacology and Toxicology, St Vincent's Hospital, Darlinghurst, NSW 2010.

Monitoring frequency for patients with renal risk factors prescribed COX-2-specific inhibitors (CSIs) or non-steroidal anti-inflammatory drug (NSAIDs)

Renal risk factors	Period of CSI or NSAID use	Suggested monitoring frequency
Nil	Short	Nil
Nil	> 2 months	1 month then yearly
Yes, and GFR 30–60 mL/min	Long or short term	1 week, 1 month, 6-monthly
Yes, and GFR < 30 mL/min and/or diabetic nephropathy and/or potassium-retaining drugs)	Long or short term	Few days, one month, 3-monthly

GFR = glomerular filtration rate.

domain. The working group acknowledged that cost should be a consideration in the prescribing decision.

The working group met four times between 11 April 2001 and 7 November 2001, and corresponded by email between meetings and up until submission of the CSI Prescribing Considerations on 30 November 2001. A comprehensive statement was prepared, which represents the consensus view of group members and was the source document (to be published separately) for this summary paper.

The key points identified by that process and a set of "considerations" relevant to the use of these new anti-inflammatory agents are presented here. The considerations are not claimed to be the result of a systematic review, but represent an extensively debated consensus view. These are not guidelines on the appropriate management of musculoskeletal disorders, but a guide to the safe use of CSIs. Some contributors removed themselves from the working group because of concerns about the prescribing considerations summary (see end of article).

The group's broad conclusion was that NSAIDs and CSIs are equivalent in efficacy as anti-inflammatory agents. The major difference is a reduced risk of clinically significant upper GI complications with CSIs.[1-6] Renal adverse event rates are similar to those with conventional NSAIDs,[7-11] and it should be noted that cardiovascular safety of CSIs remains subject to debate. We recommend that all patients prescribed CSIs or NSAIDs who need continuing treatment should be reviewed within the first few weeks of therapy to assess effectiveness and identify adverse effects. Further, the need for continuing treatment should be reviewed at regular intervals

Upper-gastrointestinal problems

CSIs are associated with considerably fewer peptic ulcers, and slightly fewer upper GI symptoms (such as dyspepsia), compared with non-selective, conventional NSAIDs. Published studies report an approximate halving of serious upper GI complications, notably bleeding, although in one major study this difference was not statistically significant,[1] and an FDA analysis of the entire study results showed less advantage for the CSI.[12] The other major study excluded patients with CV risk factors,[2] which may be significant.

However, if patients taking aspirin (eg, for prophylaxis or treatment of thromboembolic disorders) are given CSIs for arthritis symptoms, then the GI advantages of CSIs may be lost. Studies have shown that the GI advantages of CSIs may persist for up to nine months,[2] but few data are available for longer periods.[5,6] Risk factors for serious upper GI bleeding complications, such as age over 65 years, previous history of peptic ulceration, concomitant medications such as aspirin or anticoagulants and cardiovascular disease, apply equally to CSIs and NSAIDs.

It is important to note that use of CSIs does not eliminate the occurrence of ulcers or their serious complications. Monitoring for the development of an ulcer or ulcer complication is particularly indicated in patients with risk factors and should include:

- educating patients about the symptoms of GI bleeding;
- monitoring for new or severe upper-GI symptoms; and
- possibly performing baseline and periodic haemoglobin concentration measurement.

Renal

There is limited evidence about the exact effects of CSIs on renal function. However, overall, there appear to be no significant differences from conventional NSAIDs. Therefore, similar precautions and contraindications apply to both drug groups. An absolute contraindication for their use is the presence of hyperkalaemia. Caution is required for those patients with renal risk factors, which include age over 60 years, glomerular filtration rate (GFR) $\leqslant$ 60 mL per minute, patients on salt-restricted diets, those receiving diuretics, angiotensin-converting enzyme inhibitors, angiotensin-2 receptor blockers, cyclosporin, aspirin and patients with cirrhosis or congestive heart failure. These patients are at a higher risk of deterioration of renal function if CSI or NSAID therapy is prescribed.

Plasma sodium, potassium and creatinine levels, blood pressure, the presence of oedema, and urinalysis should be monitored as in the Box.

A 20% fall in GFR, provided the total GFR remains greater than 20 mL per minute, is an acceptable "trade-off", provided there is a good clinical response to these drugs.

Cardiovascular

As with NSAIDs, blood pressure may rise, sometimes substantially, with prescribing of CSIs. Blood pressure should be monitored and the dose of antihypertensive medication adjusted to maintain blood pressure at treatment target levels. CSIs, like NSAIDs, can exacerbate cardiac failure. Occasional patients may present with pulmonary oedema.

There is evidence that rheumatoid arthritis (RA) may be a risk factor for cardiovascular disease.[13] A large, long-term clinical trial in RA, using supratherapeutic doses of rofecoxib, showed an increase in the rate of myocardial infarction compared with naproxen. The reason for this difference is under debate. An increased rate of myocardial infarction has not been shown in other clinical trials of CSIs. Therefore, until there is more definitive information, we

advocate caution when considering the use of CSIs in patients with risk factors for coronary disease, especially in those with RA.

COX-2-specific inhibitors, comorbidities and coprescribed medications

The use of CSIs also needs careful consideration in other situations in which NSAIDs have caused concern.

Inflammatory bowel disease

COX-2-specific inhibitors (and NSAIDs) should be used with caution in patients with inflammatory bowel disease because of the risk of exacerbating the disease.

Respiratory disorders

Aspirin-induced asthma is an uncommon but very important manifestation of aspirin and NSAID hypersensitivity. It occurs more frequently in patients with asthma who have nasal polyps. Initial studies suggest that CSIs are safe in patients with aspirin-induced asthma, the disorder appearing to be linked to COX-1 inhibition.[14] However, great caution is recommended. If CSI use is contemplated in patients with known or suspected aspirin-induced asthma, titrating up from an initially small dose and monitoring for any exacerbation of respiratory symptoms is strongly recommended.

Hypersensitivity and sulfonamide allergy

The product information for celecoxib lists sulfonamide allergy as a contraindication. Available data suggest an overall low incidence of hypersensitivity reactions with celecoxib, but occasional cases of hypersensitivity reactions, such as urticaria, angio-oedema and Stevens–Johnson syndrome, have been described with both celecoxib and rofecoxib.

Pregnancy

Given the diverse recorded and potential effects of NSAIDs (and, by implication, CSIs) in pregnancy, such as premature closure of the ductus arteriosus and pulmonary hypertension, it is recommended that these agents be discontinued when pregnancy is contemplated or confirmed, and therapeutic use in pregnancy be managed by obstetricians or other physicians with particular expertise.

Coprescribing

Warfarin: Although a double-blind study showed that celecoxib did not affect steady-state warfarin concentrations or prothrombin time in patients taking warfarin,[15] there have been postmarketing surveillance data and published reports[16,17] of excessively prolonged prothrombin times after the introduction of both celecoxib and rofecoxib. Therefore, careful and more frequent monitoring of prothrombin time is required in patients stopping or starting CSI therapy in conjunction with warfarin therapy.

Methotrexate: CSIs have little effect on the plasma concentrations of methotrexate commonly seen in the treatment of patients with rheumatic diseases. However, there is not enough trial data available in the elderly with renal impairment, so caution should increase in older patients and patients with renal impairment.

Angiotensin-converting enzyme (ACE) inhibitors and other antihypertensive drugs: On average, a small attenuation of the antihypertensive effects of ACE inhibitors of the order of an increase in mean arterial pressure of 3 mmHg is expected with commencement of therapy with a concomitant CSI or NSAID. Similar effects are likely with other classes of antihypertensives. Combinations of ACE inhibitors, diuretics and a CSI or NSAID might have an increased risk for acute renal failure. The important point is that the blood pressure and kidney function should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

Lithium: Closer monitoring of plasma lithium concentrations is advised when stopping or starting a concomitant CSI (or NSAID), as increased lithium concentrations can occur when a CSI is added to lithium.

Final point

Prescribers should remember that CSIs are symptom-modifying drugs and do not alter the course of musculoskeletal disease, so benefits to patients must outweigh potential risks. This is a rapidly changing field and these considerations may require modification as new data emerge.

Competing interests

The working group was composed primarily of rheumatologist members of the advisory boards of the pharmaceutical companies involved in developing and marketing celecoxib and rofecoxib. Some had dual advisory board membership or other affiliations; some had no advisory roles relevant to COX-2-specific inhibitors. Advisory roles, other than employment by a pharmaceutical company, are detailed in the list of working party members at the end of this article (see footnote).

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The Australian CSI Working Group

David R Barraclough, Deputy Head, Rheumatology Unit, Royal Melbourne Hospital, VIC.*
James V Bertouch, Chairman, Department of Rheumatology, Prince of Wales Hospital, Sydney, NSW, and Chair ARA Therapeutics Committee.*,†
Peter Brooks, Executive Dean, Faculty of Health Sciences, University of Queensland, QLD.†
Mark A Brown, Director of Nephrology & Cardiology, St George Hospital, Sydney, and Professor of Medicine, University of NSW, Sydney, NSW.
Leslie G Cleland, Senior Director of Rheumatology, Royal Adelaide Hospital, and Clinical Professor, Faculty of Medicine, Adelaide University, Adelaide, SA, and Scientific Director, AFA.*
Laurie E Clemens, Director of Rheumatology, St Vincent's Hospital, Melbourne, and Senior Associate, Department of Medicine, University of Melbourne, VIC, and President, ARA.†
Steven J Crowley, Senior Manager, Reimbursement and Pricing, Healthcare Strategy & Corporate Affairs, Merck, Sharp & Dohme, Australia.
Richard O Day, AM, Professor of Clinical Pharmacology, and Director, Clinical Pharmacology and Toxicology, St Vincent's Hospital, and University of NSW, Sydney, NSW, and Member, National Prescribing Service Publications Committee.*,†
Julien P DeJager, Rheumatologist, Goldcoast Hospital, Southport, QLD, and Honorary Secretary, ARA.*,†
John P Edmonds, Director, Department of Rheumatology, St George Hospital, and Professor of Rheumatology, University of NSW, Sydney, NSW.*
Peter J Fletcher, Director of Cardiovascular Department, John Hunter Hospital, and Professor of Cardiovascular Medicine, University of Newcastle, NSW.
Gary R Franks, General Practitioner, Sydney, and Chairman, St George Division of General Practice, Sydney, NSW, and GP Consultant to the National Prescribing Service.*
David C Harris, Associate Professor of Medicine, University of Sydney, and Director of Dialysis, Western Sydney, Department of Nephrology, Westmead Hospital, Sydney, NSW.
John D Horowitz, Director of Cardiology, Northwestern Adelaide Health Services, and Professor of Cardiology, Adelaide University, Adelaide, SA.
Michael D Johnston, General Practitioner, Sydney, NSW.
Stephen J Kerr, Decisions Support Officer, National Prescribing Service, Sydney, NSW.
Geoff O Littlejohn, Director of Rheumatology, Southern Health, Monash Medical Centre, and Associate Professor of Medicine, Monash University, Melbourne, VIC.†
Graham J MacDonald, Director of Medical & Scientific Affairs, Merck, Sharp & Dohme (Australia).
Geoff J McColl, Clinical Dean, Faculty of Medicine, Dentistry & Health Sciences, University of Melbourne, and Rheumatologist, Royal Melbourne Hospital, Melbourne, VIC, and Secretary, ARA Therapeutics Committee.*
Phillip N Sambrook, Director of Rheumatology, Royal North Shore Hospital, Sydney, and Florence & Cope Professor of Rheumatology, University of Sydney, NSW, and Asia Pacific Arthritis & Rheumatism Council (funded by Pharmacia/Pfizer).†
Sepehr Shakib, Clinical Pharmacologist, Flinders Medical Centre, Adelaide, SA.
Murray W Verso, General Practitioner, Melbourne, VIC, and Merck Sharp & Dohme General Practitioner Faculty.
Neville D Yeomans, Professor of Medicine, University of Melbourne, and Head of Gastroenterology, Western Hospital, Footscray, VIC.*,†

Individuals who withdrew from the Working Group and their reasons

Individual and affiliations	Reason
Rachelle Buchbinder, Associate Professor, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, and Head, Department of Clinical Epidemiology, Cabrini Hospital, Melbourne, VIC **Marissa N Lassere,** Senior Lecturer in Medicine, University of NSW, Sydney, and Rheumatologist, St George Hospital, Sydney, NSW	*"We disagree with the GI [gastrointestinal] summary. The clear benefits of COX-2-specific inhibitors regarding clinically significant upper GI complications cannot be substantiated with current evidence."*
Craig J Eagle, Associate Medical Director, Pfizer Australia **Christopher G Fenn,** Area Medical Director (Australia/South East Asia), Pharmacia **William Lam,** Medical Director, Pfizer Australia **Michael Ortiz,** Manager for Health Outcomes, Medical Department, Pfizer Australia	*"We do not support the final version of the consensus guidelines because of the implications of certain statements on the definition of a CSI and the inconsistency with the current PI [product information] of celecoxib."*
Paddy S Hanrahan, Rheumatologist, Sir Charles Gairdner Hospital, Perth, WA, and Honorary Secretary, ARA†	*"Due to failure to reach consensus in the GI [gastrointestinal] section."*
Peter T Nash, Director, Rheumatology Research Unit, Nambour Hospital, and Senior Lecturer, Department of Medicine, University of Queensland, Brisbane, QLD†	*"Disagree with the summary of the GI [gastrointestinal] and thrombosis risk sections."*

* Celecoxib Australian Advisory Board. † Rofecoxib Australian Advisory Board. ARA = Australian Rheumatology Foundation. AFA = Arthritis Foundation of Australia.