Class: Non-opioid analgesic, NSAID (selective COX-2 inhibitor).

Indications: Coxibs available in tablet form are all licensed for use in osteo-arthritis and rheumatoid arthritis. Etoricoxib**,** acute gout; rofecoxib**,** acute pain; rofecoxib and valdecoxib, dysmenorrhoea. Parecoxib is licensed only for IM and IV use for postoperative pain. †Cancer pain.

Contra-indications: Known hypersensitivity to sulfonamides, inflammatory bowel disease, severe hepatic impairment (plasma albumin <25g/L or Child-Pugh score of ≥10), severe renal impairment (creatinine clearance <30ml/min), severe congestive cardiac failure (NYHA III-IV). *Although active peptic ulceration is considered a contra-indication by the Committee on Safety of Medicines (UK), analgesic need may dictate the closely monitored use of a coxib.*

Pharmacology

Coxibs selectively inhibit cyclo-oxygenase-2 (COX-2; Figure 1). They were developed specifically to reduce NSAID-induced gastroduodenal toxicity.[1] However, they are not harmless,[2-4] and the prevalence of serious non-gastro-intestinal effects is the same as for non-selective NSAIDs.[5, 6] Chemically, celecoxib and valdecoxib contain a sulfonamide moiety, and therefore carry a risk of sulfonamide-like undesirable effects.[7] In contrast, etoricoxib and rofecoxib contain a sulfone moiety, and the risk is less.

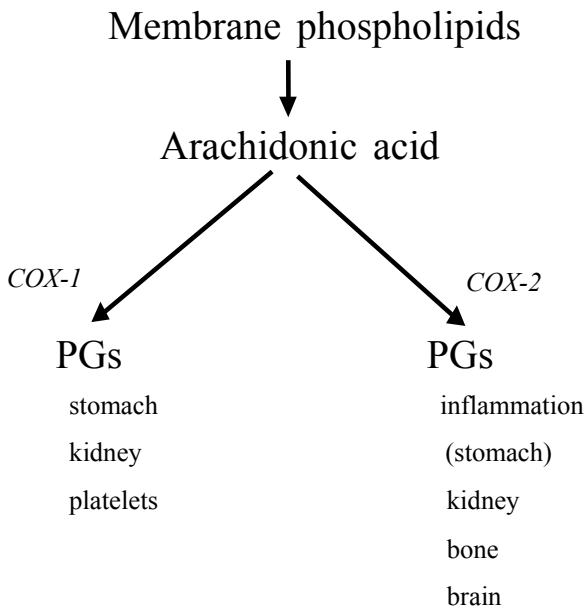


Figure 1 Cyclo-oxygenase (COX) and the production of prostaglandins (PGs).

The degree of COX-2 selectivity varies according to the assay method used and whether the result is expressed in terms of 50% or 80% inhibition of the enzyme.[8] Although 80% inhibition is theoretically a better comparator, most studies use 50% (Table 1).

Table 1 COX-2 selectivity ratio of IC_{50} COX-1/COX-2 (human whole blood assays) [8]

Drug	*COX-2 selectivity ratio*
Etoricoxib	106
Rofecoxib	35
Valdecoxib	30
Celecoxib	7.6
Nimesulide	7.3
Diclofenac	3.0
Etodolac	2.4
Meloxicam	2.0
Indometacin	0.4
Ibuprofen	0.2
Piroxicam	0.08

Celecoxib is no more selective than **nimesulide** (not available in the UK), and not much more selective than **meloxicam** and **etodolac** (generally also classed as selective COX-2 inhibitors) and **diclofenac** (generally classed as a non-selective NSAID). However, when compared with other non-selective NSAIDs collectively, celecoxib is less gastrotoxic. [9, 10] On the other hand, when used for more than 6 months in patients with osteo-arthritis and rheumatoid arthritis, celecoxib is not significantly less gastrotoxic than **diclofenac.**[11, 12]

COX-2 is massively expressed in inflammation, and is responsible for the production of prostaglandins associated with inflammatory pain. As with non-selective NSAIDs, the coxibs exert an analgesic effect by inhibiting COX-2. In terms of efficacy in osteo-arthritis and rheumatoid arthritis, coxibs are as effective as traditional non-selective NSAIDs,[2, 13] although this has been disputed.[14] As yet, there are no published trials of their use in cancer pain.

In contrast to non-selective NSAIDs, coxibs have little or no impact on the activity of COX-1, necessary for the production of prostaglandins associated with gastroduodenal mucosal protection and platelet function. Accordingly, none of the coxibs alters platelet function, and all are associated with a 50% or more reduction in the risk of a serious gastro-intestinal event (PUB, i.e. *P*erforations, symptomatic *U*lcers, major gastro-intestinal *B*leeding). For example, for every 100 patient-years of rofecoxib 50mg daily and naproxen 1500mg daily, there will be approximately 2 versus 4.5 PUBs ($p < 0.05$).[2] In other words, about 40 patients need to be treated with rofecoxib to avoid one PUB per annum. In some controlled trials, the incidence of PUBs is no greater than placebo.[15-17]

Despite gains in terms of reduced gastro-intestinal toxicity, the *overall* incidence of serious drug events with coxibs appears not to be reduced. [5, 6] Compared with **naproxen** 1500mg per day in patients with arthritis treated for a median of 9 months, rofecoxib

50mg o.d. (twice the maximum recommended dose) was associated with an excess number of cardiac ischaemic events and deaths.[2] This may relate to a round-the-clock antiplatelet effect of **naproxen** rather than a specific prothrombotic effect of high-dose rofecoxib.[18] However, in patients with arthritis, no excess of serious cardiac events has been observed with doses of 25mg o.d. or less.[19, 20]

In ordinary circumstances, a COX-2-dependent vasodilatory and antithrombotic prostaglandin (endothelial prostacyclin) 'balances' the COX-1-dependent vasoconstricting and prothrombotic prostaglandin (platelet thromboxane A_2). Coxibs inhibit the production of endothelial prostacyclin, thereby leaving platelet thromboxane unopposed. In patients in whom there is a prothrombotic tendency (including many of those with cancer), a coxib may well increase the risk of a serious thrombotic event.[21] The Summary of Product Characteristics (SPC) for all the coxibs emphasise this possibility.

The inhibition of COX-2 also results in the loss of the prostaglandin which causes vasodilation of the renal vasculature in hypovolaemic states, thereby preserving renal function.[6, 22] Coxibs can also cause fluid retention with pedal oedema, increased blood pressure (particularly in hypertensive patients),[23] and congestive cardiac failure (particularly in those with ischaemic heart disease).[5, 6]

NSAIDs delays bone healing in laboratory animals,[24, 25] and is the reason why some orthopaedic departments prohibit their use for up to 6 weeks postoperatively. The impact is greater with celecoxib and rofecoxib than with non-selective NSAIDs. In contrast, clinical studies are inconclusive.[24, 25] Thus, in a study of spinal fusion in humans, the incidence of non-union was no greater with celecoxib and rofecoxib than with placebo.[26]

Several studies confirm that coxibs are much less likely than non-selective NSAIDs to be associated with hypersensitivity reactions in patients with known hypersensitivity to

aspirin.[27-30] The concurrent administration of low-dose **aspirin** (325mg/day) and a coxib increases the risk of gastro-intestinal bleeding.[9]

For pharmacokinetic details, see Table 2. The onset of action of parecoxib ranges from 20-40min. The peak plasma concentration of its active metabolite (valdecoxib) occurs after 30-60min, and the stated duration of action is 6-12h.[31]

Table 2 Pharmacokinetic characteristics of coxibs [32-35]

	Celecoxib	*Etoricoxib*	*Rofecoxib*	*Valdecoxib*
Bio-availability	99%	~100%	93%	83%
Onset of action	**?**	24min	<45min	<30min
Time to peak plasma concentration	2–3h	1h	2–4h	~3h
Plasma halflife	8–12h	~22h	~16h	8–11h
Duration of action	12-24h	24h	24h	24h

Cautions

History of allergic-type reactions (asthma, acute rhinitis, nasal polyps, angioedema, urticaria) with **aspirin** or other NSAID. Other risk factors are listed in Box A.

Box A Risk factors for NSAID-induced serious gastro-intestinal event[36]
Age: ≥ 65 years, particularly ≥75 years
Concurrent use of a corticosteroid
Concurrent use of low-dose aspirin
Concurrent use of anticoagulant (warfarin or heparin)
Platelets <50 x 10^9/L
Acid dyspepsia with non-selective NSAID +/- PPI or coxib now or in past
Peptic ulcer in last year confirmed by endoscopy
Gastro-intestinal haemorrhage in last year confirmed by endoscopy, or strong clinical suspicion, e.g. haematemesis, melaena.

Patients already receiving **warfarin** should have their INR closely monitored during the first week after starting treatment with a coxib; increases of up to 60% have been reported.[3, 37] Patients with hypertension[23] and with cardiac, hepatic or renal impairment may deteriorate, and should be monitored appropriately. Except in patients expected to die in a few days, dehydrated patients should be rehydrated when starting treatment with a coxib (or other NSAID).

Important drug interactions

NSAIDs, including coxibs, decrease the renal excretion of **lithium**. Coxibs may reduce the renal clearance of **methotrexate**.

Cytochrome P450

Celecoxib: predominantly metabolised by CYP2C9; in patients receiving **fluconazole** (but not **ketoconazole**), the dose of celecoxib should be halved. Inducers of CYP2C9

(e.g. **barbiturates**, **carbamazepine**, **rifampicin**) may reduce plasma concentrations of celecoxib. Celecoxib inhibits CYP2D6 and may lead to increased plasma concentrations of **beta-adrenoceptor antagonists**,[38] **tricyclic antidepressants**, **SSRIs**, **antipsychotics**, and **dextromethorphan**.

Etoricoxib: metabolised mainly by CYP3A4, and plasma concentrations may be increased if co-administered with **ketoconazole** (but not **fluconazole**). CYP1A2, CYP2D6, CYP2C9 and CYP2C19 may also be involved. **Rifampicin** reduces the plasma concentration of etoricoxib by about 2/3.

Rofecoxib: metabolised mainly by reduction to dihydrorofecoxib and is therefore independent of the cytochrome P450 system. However, potent inducers of cytochrome P450 (e.g. **barbiturates**, **carbamazepine**, **rifampicin**) activate an alternative metabolic pathway. Thus, **rifampicin** reduces the plasma concentration of rofecoxib by about 1/2.

Valdecoxib (and parecoxib): metabolised mainly via CYP2C9 and CYP3A4. Plasma exposure (AUC) is increased by nearly 2/3 when co-administered with **fluconazole** (CYP2C9 inhibitor) and more than 1/3 by **ketoconazole** (CYP3A4 inhibitor). A reduction in plasma exposure (AUC) may occur with inducers of CYP3A4, particularly **rifampicin**, and to a lesser extent with **dexamethasone**, **carbamazepine** and **phenytoin**.

Undesirable effects

All coxibs can cause fluid retention, pedal oedema and hypertension. Other common effects are shown in Table 3. Celecoxib and valdecoxib are associated with sinusitis and other upper respiratory tract infections, and valdecoxib with cough and urinary tract infection. Celecoxib is also associated rarely with sulfonamide-like effects, e.g. Stevens-Johnson syndrome and toxic epidermal necrolysis (5 cases per million-patient years).

Table 3 Common (≥1/100, <1/10) undesirable effects

	Celecoxib	*Etoricoxib*	*Rofecoxib*	*Valdecoxib*
Anaemia	-	-	+	+
Insomnia	+	-	-	+
Somnolence	-	-	-	+
Dizziness	+	+	+	-
Headache	-	+	+	-
Dyspepsia/nausea	+	+	+	+
Diarrhoea	+	+	+	+
Dry mouth	-	-	-	+
Pruritus	-	-	+	+
Rash	+	-	-	+
Asthenia/fatigue	-	+	-	-
Flu-like symptoms	-	+	-	-
ALT, AST increased	-	+	+	-

The common undesirable effects with parecoxib differ from the other coxibs, possibly because use is generally short-term in post-operative patients; they include hypotension, hypokalaemia, oliguria, increased plasma creatinine concentration, respiratory insufficiency, agitation and hypaesthesia, and back pain.

Dose and use

At present, we regard rofecoxib as the coxib of choice.

In 2001, the National Institute for Clinical Excellence UK (NICE) recommended that, in patients with rheumatoid arthritis and osteoarthritis, COX-2 selective inhibitors should:

- *not* be used routinely, particularly in those with cardiovascular disease
- be used in preference to non-selective NSAIDs when there is a clear history of peptic ulcer, perforation or gastro-intestinal haemorrhage. In these patients, even the use of COX-2 selective inhibitors should be considered very carefully
- be used in preference to non-selective NSAIDs for other patients at *high risk* of a serious gastro-intestinal event (Box B).

Most patients with advanced cancer or other end-stage disease will be 'high risk' if 65 years is used as the dividing line between low and high risk on the basis of age.

For oral doses of coxibs, see Table 4. Parecoxib is administered postoperatively IM or IV 40mg stat, and then 20-40mg q6h-q12h; the maximum recommended daily dose is 80mg.

Table 4 Oral dose for licenced indications of coxibs

	Celecoxib	*Etoricoxib*	*Rofecoxib*	*Valdecoxib*
Osteoarthritis	100-200mg b.d.[a]	60mg o.d.	12.5-25mg o.d.	10-20mg o.d.
Rheumatoid arthritis	100-200mg b.d.[a]	90mg o.d.	25mg o.d.	10-20mg o.d.
Acute gout	-	120mg o.d.[b]	-	-
Acute pain	-	-	50mg stat, then 25-50mg o.d.	-

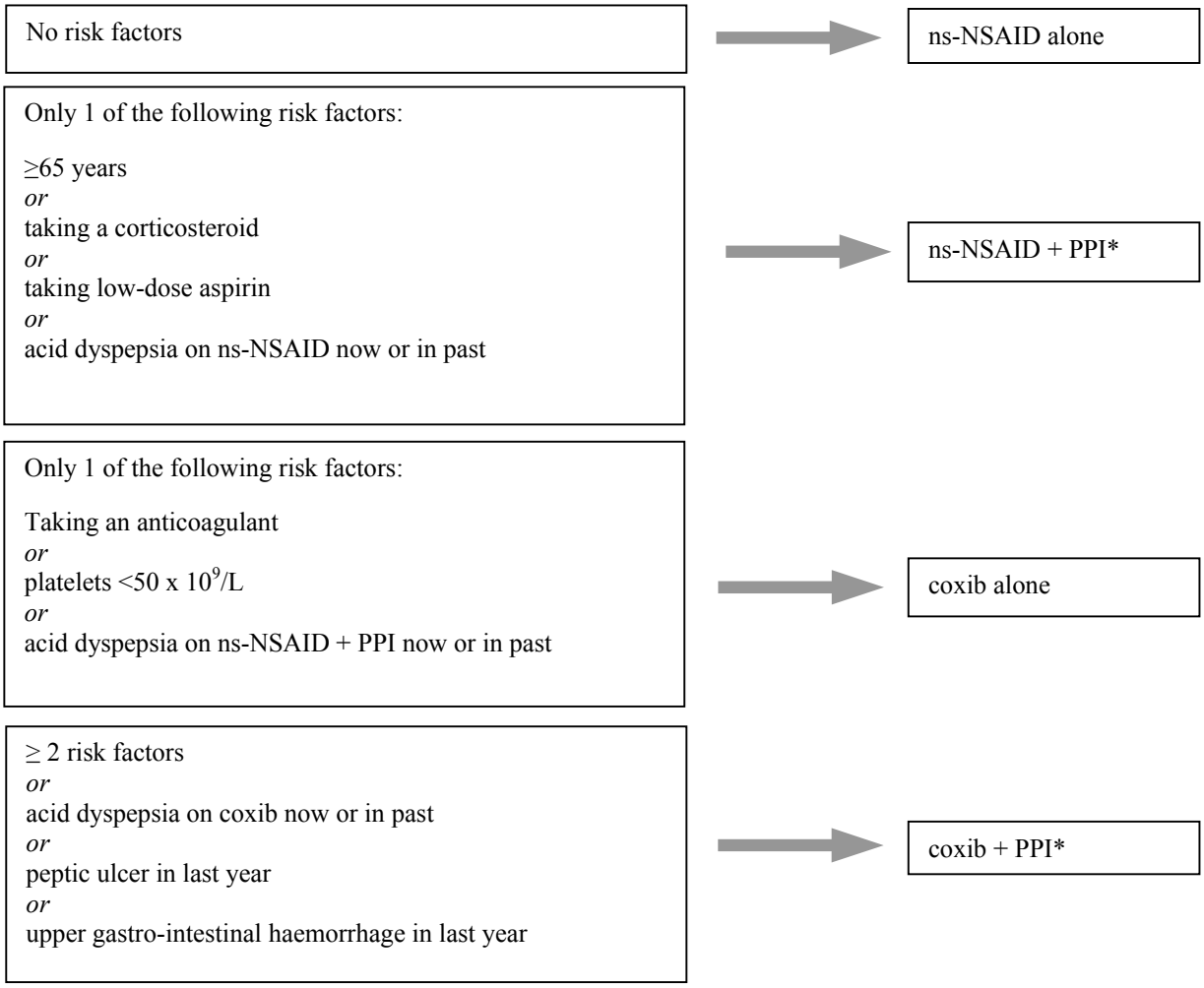
a. Total daily dose may be taken as a single dose o.d. if preferred

b. Should be used only during the acute symptomatic period

Box B Guidelines for choice of NSAID[a]

Risk factors for NSAID-related gastro-intestinal haemorrhage

1. Age ≥65 years
2. Taking a corticosteroid
3. Taking low-dose aspirin
4. Taking an anticoagulant (warfarin or heparin)
5. Platelets <50 x 10^9/L
6. Acid dyspepsia on ns-NSAID +/- PPI or coxib now or in past
7. Peptic ulcer in last year confirmed by endoscopy
8. Gastro-intestinal haemorrhage in last year confirmed by endoscopy, or strong clinical suspicion, e.g. haematemesis, melaena



Key

ns-NSAID, non-selective NSAID, e.g. diclofenac, flurbiprofen, ibuprofen, naproxen
PPI, proton pump inhibitor, e.g. lansoprazole
* if adverse reaction to PPI, substitute an H_2-receptor antagonist, e.g. ranitidine

a. Modified from Guidelines in use at Sobell House, Oxford, UK

Supply

Celecoxib

Celebrex® (Pharmacia 01304 616161)

Capsules 100mg, 200mg, 28 days @ 100mg b.d. or 200mg o.d. = £20.11.

Etoricoxib

Arcoxia® (MSD 01992 467272)

Tablets 60mg, 90mg, 120mg, 28 days @ 60mg or 90mg o.d. = £22.96.

Rofecoxib

Vioxx® (MSD 01992 467272)

Tablets 12.5mg, 25mg, 28 days @ 12.5mg or 25mg o.d. = £21.58.

Oral suspension sugar-free 12.5mg/5ml, 25mg/5ml, 28 days @ 12.5mg o.d. or 25mg o.d. = £21.58Vioxx® Acute (MSD 01992 467272)

Tablets 25mg, 50mg, 28 days @ 25mg or 50mg o.d. = £21.56; *licensed for acute pain only*.

Valdecoxib

Bextra® (Pfizer 01304 616161)

Tablets 10mg, 20mg, 40mg, 28 days @ 10mg or 20mg o.d. = £21.58.

Parecoxib

Dynastat® (Pharmacia 01304 616161)

Injection (powder for reconstitution), parecoxib (as sodium salt) 40mg vial = £4.96, 40mg vial (with solvent) = £5.67.

References

1. Flower R (2003) The development of COX2 inhibitors. *Nature Reviews.* **2:** 179-191.
2. Bombardier C *et al.* (2000) Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *New England Journal of Medicine.* **343:** 1520-1528.
3. Verrico M *et al.* (2003) Adverse drug events involving COX-2 inhibitors. *Annals of Pharmacotherapy.* **37:** 1203-1213.
4. Mamdani M *et al.* (2004) Gastrointestinal bleeding after the introduction of COX 2 inhibitors: ecological study. *British Medical Journal.* **328:** 1415-1416.
5. Wright J (2002) The double-edged sword of COX-2 selective NSAIDs. *Canadian Medical Association Journal.* **167:** 1131-1137.
6. McQuay H and Moore R (2003) Side effects of COX-2 inhibitors and other NSAIDs. In: Dostrovsky J *et al.* (eds). *Proceedings of the 10th Word Congress on Pain.* IASP, Seattle, pp. 499-510.
7. Wiholm B (2001) Identification of sulfonamide-like adverse drug reactions to celecoxib in the World Health Organization database. *Current Medical Research and Opinion.* **17:** 210-216.
8. Riendeau D *et al.* (2001) Etoricoxib (MK-0663): Preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. *Journal of Pharmacology and Experimental Therapeutics.* **296:** 558-566.
9. Deeks J *et al.* (2002) Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis; systematic review of randomised controlled trials. *British Medical Journal.* **325:** 619-623.
10. Mamdani M *et al.* (2002) Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. *British Medical Journal.* **325:** 624-627.
11. Bombardier C (2002) An evidence-based evaluation of the gastrointestinal safety of coxibs. *American Journal of Cardiology.* **89 (supplement):** 3d-9d.
12. Juni P *et al.* (2002) Risk of myocardial infarction associated with selective COX-2 inhibitors: questions remain. *Archives of Internal Medicine.* **162:** 2639-2640.
13. Silverstein F *et al.* (2003) Gastrointestinal toxicity with celecoxib versus nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *Journal of the American Medical Association.* **284:** 1247-1255.
14. McCormack K and Twycross R (2001) Are COX-2 selective inhibitors effective analgesics. *Pain Review.* **8:** 13-26.
15. Laine L *et al.* (1999) A randomized trial comparing the effect or rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology.* **117:** 776-783.

16. Lanza F *et al.* (1999) Specific inhibition of cyclooxygenase-2 with MK-0966 is associated with less gastroduodenal damage than either aspirin or ibuprofen. *Alimentary Pharmacology and Therapeutics.* **13:** 761-767.

17. Hawkey C *et al.* (2000) Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis. *Arthritis and Rheumatism.* **43:** 370-377.

18. Konstam M *et al.* (2001) Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation.* **104:** 2280-2288.

19. Ray W *et al.* (2002) COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet.* **360:** 1071-1073.

20. Reicin A *et al.* (2002) Comparison of cardiovascular thrombotic events in patients with osteoarthritis treated with rofecoxib versus nonselective nonsteroidal anti-inflammatory drugs (ibuprofen, diclofenac, and nabumetone). *American Journal of Cardiology.* **89:** 204-209.

21. Crofford L *et al.* (2000) Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase 2 inhibitors. A report of four cases. *Arthritis and Rheumatism.* **43:** 1891-1896.

22. Venturini C *et al.* (1998) Nonsteroidal anti-inflammatory drug-induced renal failure: a brief review of the role of cyclooxygenase isoforms. *Current Opinion in Nephrology and Hypertension.* **7:** 79-82.

23. Whelton A *et al.* (2002) Effects of celecoxib and rofecoxib on blood pressure and edema in patients > 65 years of age with systemic hypertension and osteoarthritis. *American Journal of Cardiology.* **90:** 959-963.

24. Simon A *et al.* (2002) Cyclo-oxygenase 2 function is essential for bone fracture healing. *Journal of Bone and Mineral Research.* **17:** 963-976.

25. Gajraj N (2003) The effect of cyclooxygenase-2 inhibitors on bone healing. *Regional Anesthesia and Pain Medicine.* **28:** 456-465.

26. Reuben S *et al.* (2002) The effects of NSAIDs on spinal fusion. *Regional Anesthesia & Pain Medicine* **26**: 16 [abstract].

27. Stevenson D and Simon R (2001) Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *Journal of Allergy and Clinical Immunology.* **108:** 47-51.

28. Woessner K *et al.* (2002) The safety of celecoxib in patients with aspirin-sensitive asthma. *Arthritis and Rheumatism.* **46:** 2201-2206.

29. Martin-Garcia C *et al.* (2002) Safety of a cyclooxygenase-2 inhibitor in patients with aspirin-sensitive asthma. *Chest.* **121:** 1812-1817.

30. Kelkar P *et al.* (2001) Urticaria and angioedema from cyclooxygenase-2 inhibitors. *Journal of Rheumatology.* **28:** 2553-2554.

31. Karim A *et al.* (2001) A pharmacokinetic study of intramuscular (i.m.) parecoxib sodium in normal subjects. *Journal of Clinical Pharmacology.* **41:** 1111-1119.

32. Agrawal N *et al.* (2003) Single- and multiple-dose pharmacokinetics od etoricoxib, a selective inhibitor of cyclooxygenase-2, in man. *Journal of Clinical Pharmacology.* **43:** 268-276.

33. Alsalameh S *et al.* (2003) The pharmacological properties and clinical use of valdecoxib, a new cyclo-oxygenase-2-selective inhibitor. *Alimentary Pharmacology and Therapeutics.* **17:** 489-501.

34. Werner U *et al.* (2002) Investigation of the pharmacokinetics of celecoxib by liquid chromatography-mass spectrometry. *Biomedical Chromatography.* **16:** 56-60.

35. Mandal U *et al.* (2003) High performance liquid chromatographic determination of COX-2 inhibitor rofecoxib in human plasma. *Journal of the Indian Medical Association.* **101:** 486-488.

36. Hawkins C and Hanks G (2000) The gastroduodenal toxicity of nonsteroidal anti-inflammatory drugs. A review of the literature. *Journal of Pain and Symptom Management.* **20:** 140-151.

37. Brown A *et al.* (2003) An interaction between warfarin and COX-2 inhibitors: two case studies. *The Pharmaceutical Journal.* **271:** 782.

38. Werner U *et al.* (2003) Celecoxib inhibits metabolism of cytochrome P450 2D6 substrate metoprolol in humans. *Clinical Pharmacology and Therapeutics.* **74:** 130-137.