National Prescribing Service Limited

Background Resource Document

for

Enhanced Divisional Quality Use of Medicines Program

June 2005

Target drug group: Nonsteroidal anti-inflammatory drugs

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This resource is also available electronically via the ADGP EDQUM website, accessible via password by EDQUM Divisional personnel (www.adgp.com.au).

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1. Guidelines and educational resources

Best practice guidelines

- National Health and Medical Research Council. *Evidence-based management of acute musculoskeletal pain* http://www.nhmrc.gov.au/publications/synopses/cp94syn.htm, 2003, accessed 21 October 2004.
- American College of Rheumatology Subcommittee on Rheumatoid Arthritis. *Guidelines for the Management of Rheumatoid Arthritis*. Updated 2002. http://www.rheumatology.org/publications/guidelines/raguidelines02.asp?aud=mem, accessed 21 October 2004.
- Australian Medicines Handbook 2004 - chapter 15.1.1.
- Therapeutic Guidelines - Analgesics Version 4 2002.

NPS resources

NPS related program: Analgesics in Musculoskeletal Pain
Date of delivery 2003

Publications: see www.nps.org.au

- NPS News 28. *Minimising the risks of using analgesics for musculoskeletal pain* - June 2003
- NPS PPR 22. *Optimising safe and effective use of analgesics in musculoskeletal pain* - July 2003 - including prescribing feedback for individual GPs.
- NPS News 18. *Osteoarthritis—have COX-2s changed its management?* October 2001
- NPS PPR 16. *COX-2 selective NSAIDs* - December 2001 - including prescribing feedback for individual GPs.
- NPS News 37. *New drugs* – December 2004
- Rofecoxib withdrawal. *Switching patients from Vioxx.* Fact sheet - 7 October 2004

Educational materials:

- NPS case study report 27*: Management of musculoskeletal pain* – July 2003
- NPS practice visits program card. *Optimising safe and effective use of analgesics in musculoskeletal pain* July 2003 (available to NPS Facilitators delivering the program). Note: New evidence on adverse events of Cox-2 selective NSAIDs has emerged since this publication.

Further resources

- *PBS dispensing data for NSAIDs at divisional and national level* (available from NPS through a collaboration with the DoHA).
- Australian Government Department of Health and Ageing. *Schedule of Pharmaceutical Benefits* (yellow book) published quarterly.

Rofecoxib withdrawal:

- NPS. Rofecoxib withdrawal. *Switching patients from Vioxx.* Fact sheet -7 October 2004 see Appendix 2. Also available via: www.nps.org.au/resources/content/nps_factsheet_vioxx_20041001.pdf
- Therapeutic Goods Administration. Media Release. *Consumer level recall of arthritis drug* http://www.tga.gov.au/recalls/2004/vioxx.htm
- Merck Sharp & Dohme. Media conference. *Merck announces voluntary worldwide withdrawal of VIOXX®*. http://www.msd-australia.com.au/news_pdf/040930.pdf.
- Fitzgerald GA. *Coxibs and cardiovascular disease*. N Engl J Med 2004;351(17):1709-11. http://content.nejm.org/cgi/content/full/351/17/1709
- Langton PE, Hankey GJ, Eikelboom JW. *Cardiovascular safety of rofecoxib (Vioxx): lessons learned and unanswered questions*. Med J Aust 2004;181(10):524-5. http://www.mja.com.au/public/issues/181_10_151104/lan10728_fm.html
- Topol EJ. *Failing the public health--rofecoxib, Merck, and the FDA.* N Engl J Med 2004;351(17):1707-9. http://content.nejm.org/cgi/content/full/351/17/1707

Celecoxib documents:

At time of publication (June 2005) NPS does not yet have enough information to make a conclusive statement on the cardiovascular safety of celecoxib. Links to the information currently at hand are given below.

TGA *Celebrex (celecoxib) information/fact sheets for patients and medical practitioners*. April 2005
http://www.tga.gov.au (with a link to the US Food and Drug Administration website)
Latest media statement available at http://www.tga.gov.au/media/2005/050225_cox2.htm

EMEA EMEA announced regulatory action on COX-2 inhibitors on 17 Feb 2005
http://www.emea.eu.int/htms/hotpress/d6275705.htm
EMEA Q&A document.
http://www.emea.eu.int/pdfs/human/press/pr/6297805en.pdf

FDA FDA Media release on Celebrex DTC Promotion http://www.fda.gov/bbs/topics/news/2004/new01147.html
FDA Alert for Practitioners on Celebrex (celecoxib)
http://www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.htm

NHS Medicines and Healthcare Products Regulatory Agency statement
http://www.mhra.gov.uk/news/2004/celecoxib_171204.pdf

2. Drug list: Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

For the purposes of this document both conventional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 selective NSAIDs are classified as NSAIDs.

NSAIDs have analgesic, antipyretic and anti-inflammatory actions. They exert their main effect by inhibiting synthesis of pro-inflammatory prostaglandins by inhibiting cyclo-oxygenase (COX). COX is present in two forms, COX-1 and COX-2. Inhibition of COX-1 is associated with impaired gastric cytoprotection and antiplatelet effects. Inhibition of COX-2 is associated with an anti-inflammatory and analgesic action.[1]

The Schedule of Pharmaceutical Benefits August 2004 classifies NSAIDs as 'Musculoskeletal system – anti-inflammatory and antirheumatic products, NSAIDs'.

The Australian Medicines Handbook 2004 classifies NSAIDs in chapter 15.1: Drugs for osteoarthritis. Other drugs in this classification include joint lubricants.[1]

There are now 11 NSAIDs, (see Table 1) and with the recent withdrawal of rofecoxib, two COX-2 selective NSAIDs (see Table 2) listed on the PBS.

The PBS listed NSAIDs and the associated restricted benefits are shown in Tables 1 and 2. PBS codes deleted from the PBS schedule during the period July 1999- June 2004 are identified by the date of the last listing on the PBS schedule.

Table 1: Nonselective NSAIDs

Generic Name	Brand names	Strengths available	PBS codes *(last listing on PBS schedule April 05)*
Diclofenac	Voltaren, Clonac, Diclohexal, Dinac, Fenac	Oral 25 mg	1299J, *1331C (08/2000)*
		Oral 50 mg	1300K, *1332D (05/2004)*
		Rectal 100 mg	1302M
Restricted benefit 1299J, 1300K: Chronic arthropathies (including osteoarthritis) with an inflammatory component; Bone pain due to malignant disease *Unrestricted listing-1302M,1332D,1331C*			
Diflunisal	Dolobid	Oral 250 mg	1319K
		Oral 500 mg	1320L
Restricted benefit: Chronic arthropathies (including osteoarthritis) with an inflammatory component; Bone pain due to malignant disease			
Ibuprofen	Brufen, Rafen	Oral 200 mg	3198H
		Oral 400 mg	3190X, 3192B
Restricted benefit 3190X, 3198H: Chronic arthropathies (including osteoarthritis) with an inflammatory component; Bone pain due to malignant disease *Unrestricted listing- 3192B*			
Indomethacin	Indocid, Arthrexin	Oral 25 mg	2454E
		Rectal 100 mg	2757D
Restricted benefit 2454E: Chronic arthropathies (including osteoarthritis) with an inflammatory component; Bone pain due to malignant disease *Unrestricted listing- 2757D*			
Ketoprofen	Orudis, Oruvail	Oral 50 mg	*1586L (11/2002)*
		Oral 100 mg S/R	*1589P (11/2002)*
		Oral 200 mg S/R	1590Q
		Rectal 100 mg	1588N
Restricted benefit 1590Q,1586L, 1589P: Chronic arthropathies (including osteoarthritis) with an inflammatory component *Unrestricted listing-1588N*			
Mefenamic acid	Mefic, Ponstan	Oral 250 mg	1824B
Restricted benefit: Dysmenorrhoea; Menorrhagia			
Naproxen	Inza, Naprosyn, Proxen, Crysanal, Anaprox	Oral 250 mg	1674D
		Oral 500 mg	1659H
		Oral 550 mg	1795L
		Oral 750 mg (S/R)	1614Y
		Oral 1g (S/R)	1615B
		Oral 125 mg per 5 mL	*1658G (08/2002)*
		Rectal 500 mg	*1662L (08/2002)*

Restricted benefit: Chronic arthropathies (including osteoarthritis) with an inflammatory component; Bone pain due to malignant disease			
Piroxicam	Mobilis, Pirohexa, Feldene	Oral 10 mg Oral 20 mg	1895R, 1897W 1896T, 1898X
Restricted benefit: Chronic arthropathies (including osteoarthritis) with an inflammatory component			
Sulindac	Aclin, Clinoril	Oral 100 mg Oral 200 mg	2047R 2048T
Restricted benefit: Chronic arthropathies (including osteoarthritis) with an inflammatory component; Bone pain due to malignant disease			
Tenoxicam	Tilcotil	Oral 10 mg	*2104R (08/2002)*
Restricted benefit: Chronic arthropathies (including osteoarthritis) with an inflammatory component; Bone pain due to malignant disease			
Tiaprofenic Acid	Surgam	Oral 200 mg Oral 300 mg	*2102P (10/2003)* 2103Q
Restricted benefit: Chronic arthropathies (including osteoarthritis) with an inflammatory component			

Note: Aspirin is listed in the PBS schedule under Nervous system – analgesic and as an antithrombotic agent.

Table 2: COX-2 selective NSAIDs

Generic name	Brand names	Strengths available	PBS codes.
Celecoxib	Celebrex	Oral 100 mg Oral 200 mg	8439E 8440F
Restricted benefit: Symptomatic treatment of osteoarthritis; Symptomatic treatment of rheumatoid arthritis			
*** Meloxicam**	Mobic	Oral 7.5 mg Oral 15 mg	8561N 8562P
Restricted benefit: Symptomatic treatment of osteoarthritis			
Rofecoxib *(withdrawn 30 September 2004)*	Vioxx	Oral 12.5 mg Oral 25 mg Oral 12.5 mg/5 ml Oral 25 mg/5 ml	8471W 8472X 8473Y 8474B
Restricted benefit: Symptomatic treatment of osteoarthritis			

*Meloxicam is COX-2 selective only at lower doses of 7.5 mg daily. It loses its COX-2 selectivity at the higher dose of 15 mg daily[1].
N.B: In 2003-04 65% of meloxicam prescriptions dispensed on the PBS were for the 15 mg strength.

3. What do we know about current prescribing patterns?

The main indications for the use of NSAIDs are for pain relief in:[1]

- Rheumatoid arthritis including juvenile rheumatoid arthritis
- Other inflammatory arthropathies
- Acute gout
- Dysmenorrhoea
- Metastatic bone pain
- Osteoarthritis
- Headache and migraine
- Postoperative pain
- Mild-to-moderate pain due to inflammation and tissue injury
- Fever
- Renal colic

See Tables 1 & 2 for the PBS restricted benefit listings for these drugs.

- **PBS data -** see separate report (available via www.adgp.com.au)
- **BEACH data** [2, 3]
    a. Musculoskeletal disease accounted for 16.8/100 encounters.
    b. NSAIDs prescription: 4.7/100 encounters.
    c. Diclofenac sodium systemic 12th and celecoxib 14th most frequently prescribed medication in general practice.
    d. The rate of COX-2 selective NSAIDs prescribed/supplied in general practice increased significantly in the period 1999-2000 to 2001-2002 with no further increase in 2002-2003. The rate of other NSAIDs declined from 1999-2000 to 2001-2002 with rates leveling off in 2002-2003.
    e. There was an increase in the rate of COX-2 selective NSAIDs prescribed from 4/100 arthritis problems in 1999-2000 to 34/100 arthritis problems in 2001-2002 and a decrease to 31/100 in 2002-2003. At the same time, the rate of other NSAIDs prescribed, advised or supplied decreased from 35/100 arthritis problems in 1999-2000 to 18/100 in 2001-2002 indicating that there has been considerable substitution of COX-2 selective NSAIDs for other NSAIDs. These rates appeared to have stabilised during 2002/3.
    f. The medication rate of COX-2 selective NSAIDs for other musculoskeletal problems also continued to increase in 2001-2002, while the rate of all other NSAIDs decreased. These rates appeared to have stabilised during 2002/3.
- **Australian Statistics on Medicines 2001-02 (DUSC survey data):**[4]

    The ongoing survey of 150 community pharmacies nationally shows the volume of drug prescriptions in the non-subsidised categories i.e. private prescriptions and PBS prescriptions under general patient co-payment. Ibuprofen use when bought without a prescription is not included. Currently data are only available up to 2002
    http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pubs-asm.htm
    Subsidised (PBS/RPBS) use of NSAIDs including COX-2 selective inhibitors varies between individual drugs. PBS/RPBS usage for the group as a whole is 86% of the total usage (i.e. subsidised plus non-subsidised) but for some drugs PBS/RPBS usage can be as low as 63-68% (e.g. diclofenac, indomethacin, piroxicam, naproxen).

Table 3: Excerpt from Table 2 of the Australian Statistics on Medicines 2001-2

Community prescription drug use in DDDs/1000 population /day

MUSCULO-SKELETAL SYSTEM
ANTI-INFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
ANTI-INFLAMMATORY/ANTIRHEUMATIC PROD.,NON-STEROIDS

		2000	2001	2002	2002% PBS/RPBS
DICLOFENAC	PBS/RPBS	4.308	3.212	3.189	64%
M01AB05	SURVEY	2.349	1.974	1.804	
INDOMETHACIN	PBS/RPBS	1.036	0.878	0.875	63%
M01AB01	SURVEY	0.607	0.526	0.529	
KETOROLAC	(Not listed on the PBS)				0%
M01AB15	SURVEY	0.007	0.005	0.006	
SULINDAC	PBS/RPBS	0.206	0.14	0.119	87%
M01AB02	SURVEY	0.031	0.019	0.018	
MELOXICAM	PBS/RPBS	0	0	1.497	99%
M01AC06	SURVEY	0	0	0.008	
PIROXICAM	PBS/RPBS	2.014	1.279	1.121	68%
M01AC01	SURVEY	0.956	0.623	0.479	
TENOXICAM	PBS/RPBS	0.236	0.143	0.092	85%
M01AC02	SURVEY	0.041	0.027	0.018	
IBUPROFEN	PBS/RPBS	1.32	0.986	0.97	69%
M01AE01	SURVEY	0.542	0.48	0.45	
KETOPROFEN	PBS/RPBS	2.477	1.558	1.342	73%
M01AE03	SURVEY	0.965	0.574	0.441	
NAPROXEN	PBS/RPBS	4.63	3.366	3.135	64%
M01AE02	SURVEY	2.598	2.008	1.734	
TIAPROFENIC ACID	PBS/RPBS	0.281	0.168	0.137	81%
M01AE11	SURVEY	0.067	0.034	0.033	
MEFENAMIC ACID	PBS/RPBS	0.062	0.06	0.054	66%
M01AG01	SURVEY	0.03	0.033	0.027	
		2000	2001	2002	2002% PBS/RPBS
CELECOXIB	PBS/RPBS	16.142	23.257	16.793	99%
M01AH01	SURVEY	0.23	0.159	0.133	
ROFECOXIB	PBS/RPBS	0	12.704	19.285	99%

M01AH02	SURVEY	0	0.067	0.139	
Total all NSAIDs listed	PBS/RPBS	32.712	47.751	48.609	86%
	SURVEY	8.423	6.529	5.819	

DDD= Defined daily dose = calculated by the World Health Organisation on the basis of assumed average daily dose per day of the drug used for its man indication by adults. Use of DDDs allows aggregation of data for those drugs with differing daily doses.

- **Data from the General Practice Research Network:**

Kerr et al[5] reported the trends in the first two years of prescribing of COX-2 selective NSAIDs by Australian general practitioners using a retrospective analysis of deidentified patient records from GPs enrolled in the GPRN.

Of patients who received their first celecoxib prescription in the three months after its listing on the PBS, 52.6% were less than 65 years, large numbers had reasons recorded for prescription that did not comply with PBS restrictions, 46.3% had not received a prescription for any pain medication in the year before being prescribed celecoxib and 6.4% were concurrently prescribed celecoxib, a diuretic and either an ACE inhibitor or angiotensin 2 receptor antagonist (a combination that could cause renal complications). The study also reported the analysis of two additional cohorts - patients prescribed rofecoxib in the first three months after PBS listing and patients first prescribed celecoxib six months after its PBS listing. The authors concluded that the rapid early adoption of COX-2 selective NSAIDs by Australian GPs has resulted in prescribing and drug use patterns that were not in accord with quality use of medicines principles.

4. Principles of quality prescribing: NSAIDs

Appropriate choice of medicines, where a medicine is considered necessary

The latest edition of the Therapeutic Guidelines: Analgesic and the Australian Medicines Handbook should be referred to for up to date recommendations on the use of NSAIDs.

1. Paracetamol is recommended as drug of first choice in all guidelines for treatment of acute low back pain. It continues to be the drug of first choice for osteoarthritis. Paracetamol 1000 mg in a single dose compares favourably to other analgesics used commonly in acute pain (e.g. diclofenac 25 mg, ibuprofen 200 mg). Regular use of therapeutic doses of paracetamol provides relief from mild-to-moderate pain. Insufficient dosing regimens can lead to perceptions of ineffectiveness.
2. If pain relief with paracetamol is inadequate consider adding or substituting an NSAID, or adding a weak opioid (such as codeine) to paracetamol or an opioid-like analgesic i.e. tramadol.[8]
3. Approximately 60% of patients will respond to some degree to any NSAID. There is little difference in anti-inflammatory efficacy between different NSAIDs. Choice of NSAID should depend on patient response and tolerance to a particular agent[1] and the cheapest and safest NSAID that the patient will tolerate.[8]
4. COX-2 selective NSAIDs are not more effective analgesics than conventional NSAIDs.
5. COX-2 selective NSAIDs are recommended for patients who are[8]:
    - not responding to conventional NSAIDs
    - at risk of gastrointestinal toxicity due to having this complication in the past
    - aged over 65 years
    - taking large doses of NSAIDs.
6. Instruct patient on *regular* analgesic use rather than as *needed.*
7. Inadequate pain relief can result in the patient progressing from acute pain to chronic pain. Review the effectiveness of analgesia regularly to minimise the risk of this occurring.

Safe and effective use

1. Adverse effects or toxicity with paracetamol are rare at therapeutic doses. It may be used in all age groups and is preferred to NSAIDs for mild-to-moderate pain as it has fewer adverse effects. To minimise risk of paracetamol toxicity, use with caution in patients:

- Fasting, with concurrent illnesses (fever, vomiting, diarrhoea) causing dehydration, or with chronic under nutrition.
- With underlying hepatic impairment or metabolic disorders.

2. All COX-2 selective and conventional NSAIDs can cause serious gastrointestinal (GI) events (bleeding, obstruction, and perforation). Risk of serious GI events is influenced by:
   - Dose and duration: Risk increases with dose and duration of exposure.[1, 9]
   - Patient characteristics: Risk greatest in people aged ≥ 65 years, history of peptic ulcer or upper GI bleeding, presence of serious co-morbidity, or concurrent use of corticosteroids or anticoagulants.[9]
   - Specific drug: Risk of serious GI events varies among drugs.[9] It is best to avoid high risk drugs (see Table 4).
3. To minimize the risk of GI events, prescribe NSAIDs and COX-2 selective NSAIDs with relatively lower risk. Table 4 classifies NSAIDs and COX-2 selective NSAIDs according to risk of serious GI events:

Table 4: Relative risk of serious gastrointestinal events*[1, 10, 11]

Lower risk
diclofenac, ibuprofen, celecoxib, rofecoxib
Medium risk
diflunisal, indomethacin, naproxen, sulindac
Higher risk
ketoprofen, piroxicam

*Meloxicam not included as no comparable GI safety clinical outcome trials- for further information see Appendix I.

4. Assess, document and regularly review pain.
    - Screen for physical and psychosocial risk factors that will influence pain.
    - Pain is subjective so measuring pain must rely upon a patients report. It has been shown that doctors tend to underestimate patient's pain severity in cancer pain management.[6] Carers tend to overestimate the pain relief required compared with the patient.[7] Judgement by the patient rather than the doctor or carer is therefore the ideal.
    - Visual analogue scales can be a sensitive and consistent means of gauging pain severity.

5. Improved GI safety of COX-2 selective NSAIDs has been questioned, particularly with celecoxib use that exceeds 6 months.
    - CLASS study did not show difference in rate of serious GI events between celecoxib, ibuprofen or diclofenac at either 6 or 12 months.[11] An advantage in favour of celecoxib was evident only when the primary endpoint (clinically significant upper GI adverse events such as bleeding, perforation or obstruction) was combined with the secondary endpoint (symptomatic ulcers as assessed by endoscopy or X-ray).
    - However, a lower incidence of serious GI events with rofecoxib than naproxen was shown in the VIGOR study.[12]
    - The trial data suggests that around 130 patients must be treated with a COX-2 selective NSAID for one year to prevent one serious gastrointestinal complication that might have developed with a conventional NSAID.[11, 12]
    - Patients at high risk have about a 5% chance annually of developing a serious gastrointestinal complication. Therefore in these patients at higher absolute risk, the potential benefits of COX-2 selective NSAIDs are likely to be greater; around 40 high risk patients must be treated with a COX-2 selective NSAID for one year to prevent one serious gastrointestinal complication.[13]

6. Minimise risk of serious GI events with COX-2 selective and conventional NSAIDs by:
    - Using regular paracetamol first, where appropriate.[1]
    - Combining regular paracetamol with a NSAID to enable a lower dose of NSAID to be used.
    - Using the lowest effective dose for the shortest period of time.[1]
    - Prescribing a drug with a lower risk of serious GI events[1] (e.g. diclofenac).
    - Using a proton pump inhibitor 20 mg orally, daily (not listed on PBS for this indication) or misoprostol 200 μgm orally 2-4 times daily (PBS authority required in patients who have a history of peptic ulcer disease and in whom NSAID therapy is essential), with a NSAID in high risk patients who cannot avoid a NSAID.[1]
    - Avoiding concurrent use of other high GI risk drugs (e.g. corticosteroids).[9]
    - Educating patients about symptoms of GI toxicity and action to take.[14]

7. COX-2 selective and conventional NSAIDs have a similar potential to cause hypertension, congestive heart failure and acute renal impairment.[1]

8. The combined use of NSAIDs or COX-2 selective NSAIDs with ACE inhibitors and diuretics, termed the "triple whammy", is implicated in a significant number of reports of drug-induced acute renal failure to the Adverse Drug Reactions Advisory Committee (ADRAC).[15] This effect is also seen with COX-2 selective NSAIDs and angiotensin receptor antagonists.[16] Situations where problems can arise include:
    - a patient is stable on 2 of these drugs and a third is added (usually the NSAID for a short-term condition);
    - diuretic doses are increased; and
    - patients suffer from dehydration e.g. due to vomiting or diarrhoea.

9. The risk of thrombotic adverse events with COX-2 selective NSAIDs requires further investigation to establish the safety of these drugs in cardiovascular disease.[17]
    - The rate of myocardial infarction was higher with rofecoxib in the VIGOR study (0.4% vs 0.1%).[12] *Rofecoxib (Vioxx) was withdrawn worldwide with effect from 30 September 2004* following analysis of the APPROVe study which showed an increased risk for confirmed cardiovascular events, such as heart attack and stroke in the patients taking rofecoxib compared to those taking placebo beginning after 18 months of treatment.
    - In December 2004, Pfizer released new information on the cardiovascular safety of celecoxib (Celebrex). The data were based on two long-term cancer trials where celecoxib was being trialled for the treatment of adenomatous polyposis at doses of 400-800 mg per day in divided doses and had demonstrated an increased cardiovascular risk over placebo. These data about adverse event rates appear inconsistent with another current cancer treatment trial and previous trials on the use of the drug for the treatment of arthritis and pain

at doses of 100-400 mg per day. The TGA has requested that the US research data be provided to the Australian regulator immediately.

- At time of publication (June 2005) NPS does not have enough information to make a conclusive statement on the safety of celecoxib. In the interim, it is important for prescribers to weigh up the risks and benefits of celecoxib for each individual and discuss this with them. The TGA has advised review for people who are taking more than 200 mg a day of celecoxib or more than 15 mg a day of meloxicam in light of an increased risk of heart attacks and strokes with high doses of these drugs. TGA has recommended that COX-2 selective inhibitors should be prescribed only when other treatments cannot be tolerated or have caused serious adverse effects and should not be prescribed for patients with increased risks of cardiovascular events, such as heart attacks; treatment should be limited to the shortest time needed. The Product Information (released in March 2005) states that Celebrex should not be prescribed for patients at high risk of cardiovascular adverse events (including those with diabetes, hypertension, hypercholesterolaemia, known ischaemic heart disease, a first-degree relative with ischaemic heart disease, cardiac failure or who are smokers). Pfizer the manufacturer of Celebrex has, however, appealed against the changes that the TGA asked them to make to their Product Information and expects a result from their appeal in June 2005.

  Safety of celecoxib needs to be considered alongside the potential risks and benefits of other therapies. Remind doctors that paracetamol is still considered first-line treatment for osteoarthritis in doses of up to 4 g daily in divided doses. Conventional NSAIDs may be a suitable replacement for some patients but care must be taken in people at higher risk of gastrointestinal complications. It is also important to be aware that long-term safety data available for the other COX-2 selective NSAID, meloxicam are limited and that COX-2 selectivity of meloxicam is dose-dependent (meloxicam at 7.5 mg is COX-2 selective whereas at 15 mg it is not COX-2 selective).

10. Patients requiring low-dose aspirin as cardiovascular prophylaxis should continue on this therapy if a COX-2 selective NSAID is introduced.[17] Recognise that concurrent low-dose aspirin use:
    - introduces another GI risk factor[1]
    - attenuates any potential GI benefit of COX-2 selective NSAIDs.[11]

SUMMARY

- Before prescribing COX-2 selective or conventional NSAIDs, review risk of peptic ulcer, cardiac disease or renal impairment.
- COX-2 selective NSAIDs are not more effective than conventional NSAIDs and have a similar range and overall incidence of adverse effects.
- Minimise risk of serious GI events with COX-2 selective and conventional NSAIDs by:
  - Using regular paracetamol first, where appropriate.[1]
  - Combining regular paracetamol with a NSAID to enable a lower dose of NSAID to be used.
  - Using the lowest effective dose for the shortest period of time.[1]
  - Prescribing a drug with a lower risk of serious GI events.[1]
  - Using a proton pump inhibitor or misoprostol, with a NSAID in high risk patients who cannot avoid a NSAID.[1]
  - Avoiding concurrent use of other high GI risk drugs (e.g. corticosteroids).[9]
  - Educating patients about symptoms of GI toxicity and action to take.[14]

5. Limitations of the PBS dataset as a data source to review prescribing of NSAIDs

- Items priced below general patient co-payment are not collected for general patients. These are diclofenac oral, diflunisal, ibuprofen, indomethacin, ketoprofen oral, mefenamic acid, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid.
- Celecoxib, rofecoxib (now withdrawn) and meloxicam are priced over the general patient co-payment and are therefore collected for all patients.
- Ibuprofen is available 'over the counter' (i.e. without a prescription) from community pharmacies and supermarkets; diclofenac is also available 'over the counter' from community pharmacies. These data are not captured by the PBS dataset.
- Three COX-2 selective NSAIDs were listed on the PBS during the period July 2000 – June 2004. These were celecoxib (Celebrex) – August 2000; rofecoxib (Vioxx) - February 2001; and meloxicam (Mobic) – February 2002. Rofecoxib (Vioxx) was withdrawn 30 September 2004 due to safety concerns.
- Tenoxicam was last PBS listed in August 2002. Similarly diclofenac potassium oral 25 mg was last PBS listed in August 2000, diclofenac potassium oral 50mg in May 2004, tiaprofenic acid oral 200 mg in November 2003, and ketoprofen oral 50 mg and 100 mg SR in November 2002.
- A knowledge of drug prices over time is required to interpret the PBS expenditure dataset. Over the period 2000-04 there were no significant increases in the PBS cost of NSAIDs including COX-2 selective NSAIDs.
- A knowledge of drug prices relative to the level of co-payment over time is required to interpret the PBS dataset. If the level of co-payment is increased, drugs which were previously captured for general patients by the PBS dataset may fall below the level of co-payment and therefore no longer be captured for general patients. For example, diclofenac suppository was above co-payment till November 2002 and since February 2003 is under co-payment. Similarly ketoprofen suppository was above co-payment till November 2000 and since February 2001 is under co-payment.
- A knowledge of changes to the PBS authority requirements and restricted benefits is required to interpret the PBS dataset. Over the period 2000-04 there were no significant changes to the PBS authority requirements and restricted benefits of NSAIDs including COX-2 selective NSAIDs.

6. Future developments

- **New COX-2 selective NSAIDs*:** Following are the new COX-2 selective NSAIDs and TGA's proposal for their use as outlined in its media release of 14th February 2005.
  - Parecoxib (injectable): **Marketed in Australia**. TGA has proposed to cancel its registration because of the risk of cardiovascular events.

- Valdecoxib (oral): **Registered but not yet marketed in Australia**. TGA has proposed to withdraw the indication of management of arthritis. Valdecoxib has been associated with an increased risk of cardiovascular events in cardiac by-pass graft patients. The use of Valdecoxib for 5 days as an analgesic in patients without increased cardiovascular risk will remain. It is withdrawn from the market in the United States and Europe due to risk of serious skin reactions.
- Etoricoxib (oral) and lumiracoxib (oral): **Registered but not yet marketed in Australia**. TGA has proposed to greatly limit the approved uses of these drugs.

*At June 2005

- **Potential changes in good practice guidelines**

The current edition of Therapeutic Guideline: Analgesic Version 4 was published in 2002.

7. Cost comparison and therapeutic relativity for NSAIDs

COX-2 selective NSAIDs cost between two to three times more than conventional NSAIDs (costs from PBS Schedule August 2004). Note - variable pack sizes for NSAIDs -comparisons based on cost per pack invalid.

Table 5: NSAID cost comparison

Generic name	Strength	Quantity	Total Cost* $
Diclofenac	Oral 25 mg	100	13.46
	Oral 50 mg	50	10.79
	Rectal 100 mg	40	22.98
Diflunisal	Oral 250 mg	100	15.24
	Oral 500 mg	50	14.93
Ibuprofen	Oral 200 mg	100	9.06
	Oral 400 mg	20-100	7.60-12.44
Indomethacin	Oral 25 mg	100	7.92-10.98**
	Rectal 100 mg	40	19.60
Ketoprofen	Oral 200 mg S/R	28	15.29-17.09**
	Rectal 100 mg	40	21.34
Mefenamic acid	Oral 250 mg	50	16.31
Naproxen	Oral 250 mg	100	14.32-17.42**
	Oral 500 mg	50	13.25-15.05**
	Oral 550 mg	50	13.51-16.51**
	Oral 750 mg (S/R)	28	12.55-14.23**
	Oral 1g (S/R)	28	15.17-16.94**
Piroxicam	Oral 10 mg	50	12.72-15.47**
	Oral 20 mg	25	12.31
Sulindac	Oral 100 mg	100	14.52
	Oral 200 mg	50	13.46-16.26**
Tiaprofenic acid	Oral 300 mg	60	15.72
Celecoxib	Oral 100 mg	60	32.17
	Oral 200 mg	30	32.17
Meloxicam	Oral 7.5 mg	30	24.80
	Oral 15 mg	30	34.00
Rofecoxib	Oral 12.5 mg	30	29.56
	Oral 25 mg	30	42.87
	Oral 12.5 mg/5 ml	150ml	29.56
	Oral 25 mg/5 ml	150ml	42.87

*Total cost includes cost to the patient and the government. Items priced under general patient co-payment are paid in full by general patients whereas concessional patients pay $4.60/item (current June 05). For items priced above co-payment, general patients pay $28.60 (current June 05) and concessional patients pay $4.60.

**Price range refers to different brand prices and is covered by the brand premium policy where Commonwealth reimbursement to pharmacists is based on the lowest-priced brand. Patients pay the difference for higher-priced brands, on top of their usual patient contribution.

The PBAC Therapeutic relativity sheet below shows specific relativities and pricing comparisons between drugs within a therapeutic group.

PHARMACEUTICAL BENEFITS PRICING AUTHORITY

Therapeutic Relativity Sheets

ATC M01 – ANTI-INFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
Effective Date: 07/03 PAGE **1** OF **1**

1. Ibuprofen and indomethacin are the older nonsteroidal anti-inflammatory drugs and have traditionally been compared on an average daily treatment cost basis. Diclofenac, naproxen, ketoprofen, diflunisal, sulindac, piroxicam and tenoxicam had been considered comparable on an average daily treatment cost basis but with a premium over 1. However, in 1989, the PBAC advised that all of these (plus tiaprofenic acid) drugs can generally be considered to be of equal safety and efficacy notwithstanding individual preferences by some patients. All of the drugs in this group are thus compared on the weighted average daily treatment costs. The PBAC's advice was confirmed in 1991.
2. Dispersible piroxicam tablets were listed on the basis of no advantage compared to piroxicam capsules.
3. Diclofenac potassium was accepted as equivalent to diclofenac sodium.
4. Naproxen sodium 550mg was listed on the basis that it had no advantage over naproxen 500mg plain tablet.
5. Leflunomide was recommended for listing on the basis that it would mainly replace IM gold injections and cyclosporin. This turned out not to be the case and continued listing (and assumed cost effectiveness) was achieved through a series of price reductions to realise a total price reduction of approximately 34% compared to the initial listing prices.
6. Celecoxib was recommended on the basis of acceptable cost effectiveness compared to NSAIDs (reduced gastrointestinal side effects).
7. Rofecoxib was recommended by the PBAC on the basis of acceptable cost effectiveness compared to NSAIDs (reduced gastrointestinal side effects). The Pricing Authority recommended pricing on the basis of similar safety and efficacy compared to Celecoxib.
8. Meloxicam was listed on the basis of similar safety and efficacy to, celecoxib and rofecoxib. Pricing is reviewed on an average daily treatment cost basis. The predicted average daily dose for meloxicam was 9.21 mg.

Accessed November 2004 at:

http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pricing-therelativity.htm

Relativity Sheets show specific relativities and pricing comparisons between drugs within a therapeutic group. The relativities are usually based on PBAC advice but may also be historically based.

5. References:

1. Australian Medicines Handbook. Australian Medicines Handbook Pty Ltd; 2004 Adelaide.
2. Britt H, Miller GC, Knox S, et al. General practice activity in Australia 2002-03. Canberra: Australian Institute of Health and Welfare (General Practice series No. 14) 2003.
3. Britt H, Miller GC, Knox S, et al. General practice activity in the states and territories of Australia 1998-2003. Canberra: Australian Institute of Health and Welfare (General Practice series No. 15). 2003
4. Commonwealth Department of Health and Ageing. Australian Statistics on Medicines 2001-2. Canberra 2003.
5. Kerr, S.J., Mant A, Horn FE et al., Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners. Med J Aust, 2003. 179:403-7
6. Cleeland CS, Gonin R, Hatfield AK, et al., Pain and its treatment in outpatients with metastatic cancer N Eng J Med 1994;330:592-6.
7. McQuay HJ, Moore RA. Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review. Health Technology Assessment 1998;2:1-235.
8. Writing Group for Therapeutic Guidelines: Analgesic. Therapeutic Guidelines: Analgesic. 4th Edition. North Melbourne 2002.
9. Anonymous. Drug and Therapeutics Bulletin 2000;38:81-6.
10. Henry D, Lim LL, Garcia Rodriguez LA, 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.
11. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study [comment]. JAMA. 2000;284:1247-55.
12. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group [comment]. N Eng J Med 2000;343:1520-8.
13. Peterson WL, Cryer B. COX-1-sparing NSAIDs--is the enthusiasm justified? JAMA 1999;282:1961-3.
14. Australian Medicines Handbook. Australian Medicines Handbook Pty Ltd; 2003 Adelaide.
15. Thomas MC. Diuretics, ACE inhibitors and NSAIDs - the triple whammy. Med J Aust 2000;172:184-5.
16. Boyd IW, Mathew TH, Thomas MC. COX-2 inhibitors and renal failure: the triple whammy revisited Med J Aust 2000;173:274.
17. Cleland LG, James MJ, Stamp LK, et al. COX-2 inhibition and thrombotic tendency: a need for surveillance. Med J Aust 2001;175:214-7.
18. Micklewright R, Lane S, Linley W, et al. Aliment Pharmacol Ther 2003;17:321-32.
19. Hawkey C, Kahan A, Steinbruck K, et al. Br J Rheumatol 1998;37:937-45.
20. Dequeker J, Hawkey C, Kahan A, et al. Br J Rheumatol 1998;37:946-51.
21. Singh G, Lanes S, Triadafilopoulos G. Am J Med 2004;117:100-6.

6. Appendices:

Appendix 1: Summary of GI safety outcome trial data for meloxicam (Mobic)

Two large, short-term, randomised controlled trials have compared the tolerability of meloxicam with that of diclofenac and piroxicam. Note that the duration of these trials was only 28 days and the dose of meloxicam used was not comparable to diclofenac or piroxicam.[18]
In the MELISSA study, patients with osteoarthritis were randomised to either meloxicam 7.5mg (n=4635) or diclofenac 100 mg modified-release (n=4688) once daily for 28 days. Significantly fewer gastrointestinal adverse events (i.e. dyspepsia, nausea and vomiting, abdominal pain and diarrhoea) occurred in the meloxicam group (13% vs 19%; p< 0.001), and withdrawals due to adverse events were also lower in this group (5.5% vs 8%; p < 0.001).[19] It has been suggested that the differences in tolerability between meloxicam and diclofenac could have occurred because the doses used were NOT comparable – the efficacy ratings in the MELISSA study constantly favoured diclofenac.[18] There was no significant difference between the groups with regard to the occurrence of perforations, ulcers or bleeds, but the study was only short term and was NOT powered to show this.[18]

In the SELECT study, osteoarthritis patients were randomised to receive either meloxicam 7.5 mg (n=4320) once daily, or piroxicam 20 mg (n = 4336) once daily for 28 days.[20] Gastrointestinal adverse events were significantly lower with meloxicam (10.3% vs 15.4%; p<0.001). There was no significant difference in perforations, ulcers or bleeds, although again, the study was not powered to show this. Meloxicam was as effective as piroxicam in this study.[18]

More recently a pooled analysis of 24,196 patients funded by Boehringer-Ingelheim looking at serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam was undertaken.[21] 24 196 patients from 28 trials (published and unpublished) were included. The trials from which patients were selected are not listed or referenced. It is assumed 17 979 patients were from the MELISSA and SELECT trials outlined above. Only a small number of patients (n = 2 960) received meloxicam 15 mg daily. (PBS data suggests that 65% of meloxicam patients are prescribed. Meloxicam at a dose of 7.5 mg once daily was associated with a 0.03% risk of serious gastrointestinal events through 60 days, which was significantly lower than diclofenac 100-150 mg per day, piroxicam 20 mg per day or naproxen 1000 mg per day. At a daily dose of 15 mg meloxicam was associated with a significantly lower risk of serious gastrointestinal complications only when compared with piroxicam. The number of patients followed for more than 60 days was so small comparisons for this time period were not possible. The risk of thromboembolic events with meloxicam 7.5 mg per day was significantly lower than with diclofenac 100-150 mg per day, but was not significantly different from piroxicam and naproxen. The major limitations of the study are the use of non-comparable doses of conventional NSAIDs and the short duration of the studies included (most less than 60 days). Given the methodological limitations of the study the risk estimates for gastrointestinal and cardiovascular complications of long-term use of meloxicam are not certain.

Appendix 2: NPS Fact sheet *Switching patients from Vioxx* 7 October 2004

National Prescribing Service Limited

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Fact sheet **Updated 7 October 2004**

Switching patients from Vioxx

Merck Sharpe & Dohme has announced an immediate voluntary worldwide withdrawal of rofecoxib (Vioxx).

This follows analysis of the APPROVe study which was studying the effects of rofecoxib compared with placebo on recurrent colon polyps. The trial was stopped early for safety reasons.

There was an increased risk for confirmed cardiovascular events, such as heart attack and stroke in the patients taking rofecoxib compared to those taking placebo, beginning after 18 months of treatment. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on rofecoxib which is probably related to the frequency of the adverse event and the number of subjects in the trial, that is the statistical power.

New data

APPROVe was a multicentre, randomised, placebo-controlled, double-blind study to determine the effect of 156 weeks (three years) of treatment with rofecoxib on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenoma. The trial enrolled 2,600 patients and compared rofecoxib 25 mg to placebo. The trial began enrolment in 2000.

In this study 25 patients taking placebo versus 45 patients taking rofecoxib experienced a confirmed serious thrombotic event such as myocardial infarction or stroke. The absolute event rates were approximately 3 per 400 patient years for placebo and 6 per 400 patient years for rofecoxib - an absolute increase in risk of approximately 3 thrombotic events per 400 patient years of treatment. This means that for every 100 patients treated for 4 years, three would have a serious thrombotic event over and above what would normally be expected. The difference in event rates was only apparent after 18 months of treatment.

Changing to an alternative

People taking rofecoxib are being advised to contact their doctor to discuss switching to alternative therapy. They will not be able to get repeat prescription for rofecoxib filled.

There is no evidence currently to suggest that other COX-2 selective inhibitors will have the same effects as rofecoxib but as these effects were not seen for 18 months it is important to look at long-term data with sufficient numbers of patients for the other agents. Long-term placebo controlled studies are not currently available for other COX-2 selective inhibitors such as celecoxib and meloxicam.

The general advice from NPS regarding NSAIDs including COX 2 selective NSAIDs is to:

1. Use paracetamol as first line management when possible.
2. Use NSAIDs that are lower risk for serious gastrointestinal complications (eg celecoxib, diclofenac and ibuprofen) in preference to higher risk agents
3. Consider the adverse effect profile of the drugs in relation to the individual patient.

Potential adverse effects include:

• gastrointestinal effects.

• hypertension, heart failure and renal impairment: all NSAIDs can cause sodium and water retention, decreased glomerular filtration rate, increased blood pressure, peripheral oedema, and congestive heart failure. Caution is advised if NSAIDs or COX-2 selective NSAIDs are used in patients at risk of acute renal failure or heart failure, particularly the elderly. Assess renal function and blood pressure prior to prescribing and during therapy in those considered at risk.

• acute renal failure and 'triple whammy': As with other NSAIDs, COX-2 selective NSAIDs are associated with acute renal failure, particularly when used in combination with ACE inhibitors and thiazide diuretics.

• acute neuropsychiatric reactions, including confusion, insomnia, hallucinations, and depression, have been reported following celecoxib and rofecoxib use.

COX-2 selective NSAIDs are no more effective at relieving inflammation and pain than conventional NSAIDs.

It is important to report all suspected adverse effects to the Adverse Drug Reaction Advisory Committee (ADRAC) on their blue form.

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