**The Interpretation of the NICE Technology Appraisal No. 27: Use of Cox II Inhibitors for Osteoarthritis and Rheumatoid Arthritis, in the Context of License Changes Made in 2005.**

In July 2001 NICE issued guidance TA27 to the NHS on the use of Cox II selective inhibitors for osteoarthritis and rheumatoid arthritis. TA27 covered etodolac, meloxicam and the two then available coxibs, rofecoxib and celecoxib. A review of TA27 was initiated in August 2003.

The review was suspended in February 2005 following the withdrawal of rofecoxib and pending the outcome of an EMEA review of the safety of both Cox II inhibitors and standard NSAIDs.

The EMEA has now completed its safety review and there have been a number of resulting changes to the summaries of product characteristics (SmPCs) of the drugs included in this appraisal, please see http://www.emea.eu.int/pdfs/human/press/pr/20776605en.pdf and http://www.emea.eu.int/pdfs/human/press/pr/29896405en.pdf.

The EMEA safety review has confirmed the caution noted within TA27 related to the cardiovascular safety of the Cox II selective inhibitors. Patients and healthcare professionals should refer to the MHRA and EMEA websites for further information http://www.mhra.gov.uk/ and http://www.emea.eu.int/.

The Institute has reviewed the impact of these regulatory changes on the current NICE guidance and has concluded that TA 27 should not be withdrawn, but that healthcare professionals should be advised to take note of both the existing guidance and the current versions of the SmPCs when prescribing these drugs.

The Institute also concluded that because the regulatory changes have raised important questions concerning the role of all NSAIDs within the pathway of care, which are beyond the scope of a technology appraisal, they should be considered in the contexts of the forthcoming clinical guideline for osteoarthritis (anticipated publication June 2008) and the Institute's proposal to the Department of Health for a clinical guideline on rheumatoid arthritis. The Institute intends to consult shortly with existing consultees and commentators on this proposal.

The Institute's current guidance on the COX II inhibitors and its interpretation in the light of changes to the SmPCs is set out below.

| Guidance | | |
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| 1.1 | Cox II selective inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs) are indicated for pain and stiffness in inflammatory rheumatoid arthritis and for the | The SmPCs now state that Cox II selective inhibitors should be used at the minimum effective dose for the |

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| | short-term management of pain in osteoarthritis. All NSAIDs are associated with adverse events and should only be prescribed when there is a demonstrable clinical need and in accordance with their summary of product characteristics. Long-term use should be avoided without appropriate monitoring and re-evaluation of the clinical need. | shortest duration necessary. |
| 1.2 | Of particular concern is the propensity of NSAIDs, including the Cox II selective agents, to cause gastro-intestinal adverse events, which can include life threatening gastro-intestinal perforations, ulcers or bleeds. These agents should therefore only be prescribed after careful consideration of their risks and benefits, especially in patients who may be at increased risk of such adverse events. | Prescribers should take note of the revised contraindications and warnings in the SmPCs. |
| 1.3 | Cox II selective inhibitors are not recommended for routine use in patients with rheumatoid arthritis (RA) or osteoarthritis (OA). They should be used, in preference to standard NSAIDs, when clearly indicated as part of the management of RA or OA, only in patients who may be at ‘high risk’ of developing serious gastrointestinal adverse effects. | Prescribers should take note of the revised contraindications and warnings in the SmPCs. |

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| 1.4 | Patients at 'high risk' of developing serious gastrointestinal adverse events include those of 65 years of age and over, those using concomitant medications known to increase the likelihood of upper gastrointestinal adverse events, those with serious co-morbidity or those requiring the prolonged use of maximum recommended doses of standard NSAIDs (See Section 2.10).<br><br>The risk of NSAID-induced complications is particularly increased in patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation. The use of even a Cox II selective agent should therefore be considered especially carefully in this situation. | Etodolac and meloxicam are now contraindicated in those with a history of GI bleeding or perforation, related to previous NSAID therapy. Prescribers should take note of the revised contraindications and warnings in the SmPCs. |
| 1.5 | In all patients with cardiovascular disease, there remains uncertainty over the use of Cox II selective inhibitors and they should not therefore be prescribed routinely in preference to standard NSAIDs where these are indicated in this group of patients.<br><br>Furthermore, many patients with cardiovascular disease receive low dose aspirin and this carries an increased risk of gastro-intestinal events. In patients who are taking low dose aspirin, the benefit of using Cox II selective agents (to decrease gastrointestinal toxicity) is reduced. Prescribing Cox II selective agents preferentially over standard NSAIDs in this situation is therefore not justified on current evidence. | The EMEA safety review has confirmed the concerns about the cardiovascular safety of cox II inhibitors.<br><br>The SmPCs state that caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding. The SmPCs also note that a significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long- |

| Guidance | | |
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| | | term clinical trials. |
| 1.6 | There is no evidence to justify the simultaneous prescription of gastro-protective agents with Cox II selective inhibitors as a means of further reducing potential gastrointestinal adverse events. | The EMEA have recommended that, in line with other NSAIDS, when prescribing etodolac or meloxicam, combination therapy with gastroprotective agents should be considered in patients with a history of ulcer, those requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk. |