

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal (Review)

Cyclo-oxygenase (Cox) II selective inhibitors for osteoarthritis and rheumatoid arthritis

Scope

Objectives:

(1) to review and update if and as necessary the guidance to the NHS in England and Wales on the clinical and cost effectiveness of four selective Cox II inhibitors for the treatment of osteoarthritis and rheumatoid arthritis, which was issued in July 2001¹. The date set for review of this guidance was May 2004. The review date was set on the basis of the Institute's judgement of the pace of change in the evidence base at the time the original guidance was issued. The original guidance will remain in place unless and until any new guidance has been issued. The review will consider whether any new evidence that has become available justifies a change to the original guidance.

(2) to assess the clinical and cost effectiveness of three additional selective Cox II inhibitors for the treatment of osteoarthritis and rheumatoid arthritis (etoricoxib, valdecoxib and lumiracoxib) and to provide guidance to the NHS in England and Wales.

Background and technologies:

Osteoarthritis (OA) and rheumatoid arthritis (RA) are chronic degenerative diseases of synovial joints, leading to joint deformities, restricted movement and often chronic pain. In some individuals disease modifying agents can alter the progression of the arthritis, but treatment usually centres on symptomatic pain control for which non-steroidal anti-inflammatory drugs (NSAIDs) are widely used.

NSAIDs exert their analgesic effect by inhibition of the cyclooxygenase (Cox)-enzyme that mediates prostaglandin synthesis. At least two forms of the enzyme have been identified, termed Cox I and Cox II. It is thought that inhibition of Cox I leads to the gastrointestinal side effects that are associated with all NSAIDs. Of particular concern are perforations, obstructions, ulcers and bleeds, which can be fatal. NSAIDs vary in their relative inhibition of the two forms of the enzyme, which gives them different risk profiles for adverse gastrointestinal events. The term 'coxib' describes a group of drugs that was designed to selectively inhibit Cox II whilst 'sparing' Cox I.

In July 2001, the Institute issued guidance on the Cox II selective inhibitors etodolac, celecoxib, meloxicam and rofecoxib. At the time, rofecoxib was not

licensed for the management of RA. Since the issue of guidance, the marketing authorisation for rofecoxib has been extended to include RA, and three further coxibs, etoricoxib, valdecoxib and lumiracoxib have received marketing authorisation.

The current marketing authorisations related to OA and RA are:

- Meloxicam is indicated for short-term symptomatic treatment of exacerbations of OA and long-term symptomatic treatment of RA.
- Etodolac is indicated for acute and long-term use in RA and OA.
- Celecoxib and rofecoxib are indicated for the symptomatic relief in the treatment of OA or RA.
- Etoricoxib and valdecoxib are indicated for the symptomatic relief of OA or RA.
- Lumiracoxib is indicated for the symptomatic relief of OA.

None of these drugs are recommended in individuals under the age of 15 years.

Intervention(s)	Celecoxib, rofecoxib, meloxicam, etodolac, etoricoxib, valdecoxib and lumiracoxib as per licensed indications
Population(s)	People with OA or RA
Current standard treatments (comparators)	Non-Cox II selective NSAIDs Cox II selective NSAIDs
Other considerations:	<p>Outcomes to be considered include: efficacy, short-term and long-term adverse effects, quality of life, and cost-effectiveness.</p> <p>If the evidence allows,</p> <ul style="list-style-type: none"> • Gastrointestinal adverse effects will be analysed by the incidence of symptomatic perforations, ulcers, obstructions and bleeds. • Analysis will include the impact of concomitant gastroprotective agents, either with the intervention or the comparator. • Analysis will include the impact of concomitant therapy with low dose aspirin for prophylaxis of cardio-vascular events. • Analysis will include direct comparisons between Cox II-selective agents where available. • Analysis will take into account confounding effects such as <i>H.pylori</i> infection. <p>It is appreciated that individuals participating in clinical trials may also use non-pharmacological strategies, such</p>

	<p>as physiotherapy. Where the evidence permits, any confounding factors resulting from such non-pharmacological strategies will be taken into consideration.</p> <p>The appraisal will attempt to identify people for whom selective Cox II inhibitors are particularly appropriate or effective.</p>
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¹ *Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis (No.27, July 2001):*

- *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 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.*
- *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, ulcer 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.*
- *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 and OA only in patients who may be at 'high risk' of developing serious gastrointestinal adverse effects.*
- *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. 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 carefully in this situation.*
- *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. Furthermore, many patients with cardiovascular disease receive low dose aspirin and this carries an increase 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.*
- *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.*