

**ketoprofen/omeprazole, 100mg/20mg; 200mg/20mg modified
release capsules (Axorid®) No. (606/10)**
Meda Pharmaceuticals

05 February 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ketoprofen/omeprazole (Axorid®) is not recommended for use within NHS Scotland for the symptomatic treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis in patients with a previous history or who are at risk of developing NSAID associated gastric ulcers, duodenal ulcers and gastroduodenal erosions in whom continued treatment with ketoprofen is essential.

Studies in healthy volunteers demonstrated the bioequivalence of this combination product to the reference products, modified release ketoprofen and omeprazole.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Symptomatic treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis in patients with a previous history or who are at risk of developing NSAID associated gastric ulcers, duodenal ulcers and gastroduodenal erosions in whom continued treatment with ketoprofen is essential.

Dosing information

For adults and adolescents over the age of 15 years: 100mg/20mg to 200mg/20mg orally daily depending on the severity of symptoms.

Product availability date

January 2010

Summary of evidence on comparative efficacy

Ketoprofen/omeprazole (Axorid[®]) capsules contain a prolonged-release form of the non-selective nonsteroidal anti-inflammatory drug (NSAID) ketoprofen in combination with a gastro-resistant release form of the proton pump inhibitor (PPI) omeprazole.

The submission states that no clinical efficacy and safety studies were deemed necessary for the marketing authorisation application for Axorid[®] as both ketoprofen and omeprazole are already approved for their respective indications.

Studies in healthy volunteers demonstrated bioequivalence between the individual ketoprofen and omeprazole components and their respective reference products, (sustained release ketoprofen and omeprazole), as well as between the individual components and the fixed dose combination. Studies also showed comparable bioavailability of the individual components in the fed and fasting states.

Summary of evidence on comparative safety

There is no evidence on the comparative safety of this combination product which is indicated for a population that includes patients at higher risk of developing gastrointestinal lesions than if the two components were prescribed separately. The licensed patient population for the ketoprofen/omeprazole combination capsule includes patients with a history of recurrent peptic ulceration or chronic dyspepsia. Ketoprofen sustained release capsule is contraindicated in this high risk group.

In October 2007, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued advice that ketoprofen has been associated with a higher gastrointestinal risk than most other NSAIDs in the class. The British National Formulary (BNF) notes that ketoprofen has anti-inflammatory properties similar to ibuprofen and has more adverse effects. It cites advice from the MHRA Committee on Safety of Medicines (CSM) that among non-selective NSAIDs, ketoprofen is associated with intermediate risk of serious upper gastrointestinal adverse effects. The BNF states that the CSM contraindicates non-selective NSAIDs in patients with a history of peptic ulceration.

Summary of clinical effectiveness issues

The licensed indication targets a very specific population of patients with rheumatoid arthritis, ankylosing spondylitis or osteoarthritis who are already receiving ketoprofen and have a previous history or are at risk of developing NSAID associated gastric ulcers, duodenal ulcers and gastroduodenal erosions and in whom continued treatment with ketoprofen is essential. Currently available preparations of ketoprofen alone, however, are contraindicated in patients with a history of recurrent peptic ulceration or chronic dyspepsia.

Ketoprofen currently comprises only 0.3% of non-selective NSAID use in Scotland and it would be expected that many of these patients would already be receiving concomitant PPI treatment in line with current guidelines. There is considerable variation in individuals' tolerance and response to NSAIDs; approximately 60% of patients will respond to any NSAID and those who do not respond to one may well respond to another. The proportion of patients at high risk of gastrointestinal toxicity in whom continued treatment with ketoprofen is considered essential is unknown but is likely to be extremely small or possibly non-existent.

As well as the potential gastrointestinal toxicity, NSAIDs and cyclo-oxygenase (COX)-2 inhibitors are associated with liver and cardio-renal toxicity. Therefore it is important that gastrointestinal toxicity is not considered in isolation but that an individual patient's risk factors, including age, are assessed when selecting an NSAID/COX-2 inhibitor and its dose.

The ketoprofen/omeprazole combination product has been studied in healthy volunteers only. It has been assumed that its efficacy would be the same as the components administered separately but that its safety would be improved due to the inbuilt gastroprotective agent. The use of one combination capsule instead of two individual capsules may increase patient compliance, however there are no safety or adherence comparisons with its separate components or with other NSAIDs plus gastroprotective agents in this patient population. Also, as previously stated, it is indicated for a population that includes patients at higher risk of developing gastrointestinal lesions than the reference modified release ketoprofen product.

The manufacturer used an indirect strategy to measure the effect of an NSAID/omeprazole combination product on gastrointestinal adverse event rates and compared this with a composite NSAID plus omeprazole claimed to represent NSAID usage in Scotland. However, it was not possible to draw any valid conclusions from this due to several limitations. There was no systematic literature search and no evidence of consistency among the patient populations studied or consistency with the licensed indication.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing the combined ketoprofen/omeprazole product with an NSAID and omeprazole prescribed individually in patients with osteoarthritis (OA) or rheumatoid arthritis (RA). The NSAID was a composite or weighted average of NSAIDs used in Scottish practice. It was assumed the combined product was as effective in terms of pain control as ketoprofen alone, with the added benefit of better gastro-protection as a result of better adherence to treatment with one capsule per day instead of two. There were no clinical trials that made a direct comparison of these two options on the rate of gastrointestinal events so an indirect approach was used to compare an NSAID/omeprazole combined preparation with NSAID plus omeprazole, involving

extensive use of published research literature to estimate reductions in surgery, mortality and treatment for dyspepsia.

Utilities for different states were also taken from a published research study. Costs were taken from recognised sources. The time horizon was one year.

The submission claimed that over one year the difference in costs with the combined product compared to NSAID and PPI prescribed separately would be an extra £29.17 per patient with a gain of 0.00199 of a QALY. This gave an incremental cost-effectiveness ratio of £14,658 per QALY.

The principal weakness was that the submission appeared to interpret the licence as including most patients starting a long-term NSAID rather than the specific group of patients needing continued treatment with ketoprofen but who have a significant risk of gastrointestinal problems. As such, a more relevant comparison for the analysis could have been modified release ketoprofen and omeprazole prescribed separately. A simple analysis using this comparison would have been appropriate. In terms of the analysis that was presented, the following additional concerns were noted;

The lack of direct comparative data on GI outcomes in patients with OA, RA meant that the estimated benefits drew on over 17 different published research reports. There was no evidence these were representative of other research findings, that the patients and definitions used in different studies were compatible, or that the patients and definitions used reflected the licence or likely Scottish practice;

The utility values used were drawn from a single study, which, arguably, overstate the health loss from GI events – for example someone experiencing dyspepsia is assumed to have 50% quality of life for three months, and someone needing ulcer surgery is assumed to be in a health state equal to being dead for 3 months. Other, equally plausible, values are available that may well give a substantially different QALY result;

The cost of the standard NSAID is likely to have been overestimated because a 30 day duration was assumed for prescriptions but a prescription duration is typically 56 days.

The submission made clear that the results are highly sensitive to variables such as the effect of PPI non-compliance on GI event rate, the incidence of dyspepsia while on an NSAID, the daily NSAID cost and the arthritis utility. All of these derive from the literature search, which has not been demonstrated to be adequate.

Given all of these issues the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published national clinical guidelines for the care and management of osteoarthritis in adults in February 2008 and for the management and treatment of rheumatoid arthritis in adults in February 2009. Both guidelines recommend that oral NSAIDs/COX-2 inhibitors be used at the lowest effective dose for the shortest possible period of time and that the lowest acquisition cost PPI be co-prescribed.

Additional information: comparators

The most relevant comparator is ketoprofen MR with omeprazole prescribed separately. Other possible comparators include other NSAIDs with concomitant PPI or the fixed combination product diclofenac/misoprostol.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Ketoprofen/omeprazole MR (Axorid®)	100mg/20mg to 200mg/20mg once daily	167
NSAID plus PPI prescribed separately		
Ketoprofen MR (Oruvail®) plus omeprazole	100mg to 200mg daily plus 20mg once daily	179 to 333
Ibuprofen MR plus omeprazole	1600mg once daily plus 20mg once daily	111
Ketoprofen MR (non-proprietary) plus omeprazole	100mg to 200mg daily plus 20mg once daily	66 to 109
Naproxen plus omeprazole	250mg to 500mg twice daily plus 20mg once daily	60 to 72
Diclofenac MR plus omeprazole	75mg once or twice daily plus 20mg once daily	48 to 72
Meloxicam plus omeprazole	7.5mg to 15mg once daily plus 20mg once daily	55 to 61
Ibuprofen plus omeprazole	400mg to 800mg three times daily plus 20mg once daily	24 to 49
Diclofenac plus omeprazole	25mg to 50mg three times daily plus 20mg once daily	38 to 39
NSAID plus misoprostol combination tablets		
Diclofenac/misoprostol 50mg/200microgram combination tablet (Arthrotec 50®)	One tablet two to three times daily	145 to 218
Diclofenac/misoprostol 75mg/200microgram combination tablet (Arthrotec 75®)	One tablet twice daily	192

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 30.11.09

Additional information: budget impact

The manufacturer estimated that 285,000 patients in Scotland consult their GP for OA, RA, ankylosing spondylitis and related conditions each year, of whom 45% are prescribed an NSAID and 28.5% of whom are also prescribed gastro-protection. Based on these figures, plus estimates of incidence and numbers stopping treatment, the manufacturer estimated the potential market for the product to be 37,983 patients in year 1. The market share was estimated at 10% (3,788 patients) in year 1 rising to 50% (21,092 patients) in year 5. On this

basis, the manufacturer estimated that the net drug budget impact of switching from prescribing a weighted average NSAID and PPI individually to Axorid[®] would be £168k in year 1 rising to £931k in year 5.

SMC clinical experts indicated that these estimates of market share are highly optimistic given the current usage of ketoprofen and the restrictions imposed by the marketing authorisation for the product.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 January 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.