Scottish Medicines Consortium

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

Meda Pharmaceuticals

04 June 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 re-submission

ketoprofen/omeprazole (Axorid®) is accepted for use within NHS Scotland.

Licensed indication under review: 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.

Other nonsteroidal anti-inflammatory drugs can be co-prescribed with proton pump inhibitors at lower cost.

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

4 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, modified-release ketoprofen (ketoprofen MR) 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 while ketoprofen modified-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. Ketoprofen alone is contraindicated in patients with a history of recurrent peptic ulceration.

In the latest figures available, ketoprofen 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 the tolerance of individuals 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 would be essential is unknown, but is likely to be extremely small.

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 not been studied in the licensed patient population. It has been assumed, but not proven, that its efficacy would be the same as its separate components 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 which includes patients at higher risk of developing gastrointestinal lesions than the reference modified-release ketoprofen product.

Summary of comparative health economic evidence

The manufacturer submitted a simple cost-minimisation analysis comparing the fixed combination of ketoprofen MR and omeprazole (Axorid®) with the same two medicines prescribed separately. A one-year time horizon was used. Equivalent outcomes were assumed in all respects, based on the bioequivalence studies. The two cost components were the medicines costs and GI adverse event; however, the rates of GI events were assumed to be identical, hence this component of costs was also identical.

Treatment with the combined product was estimated to cost £144.09 per year (including treating GI events and accounting for treatment withdrawals) whereas treatment with the same medicines prescribed separately was estimated to cost £206.70. In each case, £8.70 was due to treating GI adverse events.

The sensitivity analysis supported the claim of cost saving so long as the daily cost of ketoprofen MR was above £0.397 (compared to £0.611 at baseline). The economic comparison was based on current practice, which involves reimbursement of ketoprofen MR prescriptions at a range of prices depending on the individual preparation dispensed (ketoprofen MR is not included in Part 7 of the Scottish Drug Tariff therefore a single tariff price does not exist). Cheaper versions of generic ketoprofen MR are available and it

should be noted that if the analysis was conducted against either of the two cheapest branded generic products, the combination product would no longer be preferred on cost-minimisation grounds.

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.

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	191 to 345
Ketoprofen MR (non-proprietary) plus omeprazole	100mg to 200mg daily plus 20mg once daily	86 to 146

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 26.03.10

Additional information: budget impact

The net medicines budget impact was estimated to be a saving of £1,175 in year 1 rising to a saving of £9,085 by year 5. The budget impact was based on 149 patients in year 1 rising to 165 in year 5 as the prevalence of arthritis increases over time. These figures were derived from an estimate of patients currently receiving ketoprofen MR in Scotland and an assumption that of these 28.5% would be co-prescribed gastro-protection. The share of the market, when ketoprofen MR and omeprazole were used together as Axorid®, was assumed to rise from 10% in year 1 to 100% in year 5.

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 12 April 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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.