HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

5 May 2010

XILANIK 100 mg/20 mg, modified-release capsule
B/14 (CIP: 395 731.3)

XILANIK 200 mg/20 mg, modified-release capsule
B/14 (CIP: 395 734.2)

Applicant: PIERRE FABRE MEDICAMENT

Ketoprofen, omeprazole

ATC code: M01AE53

List II

Date of Marketing Authorisation: 15 September 2009 (national procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Ketoprofen, omeprazole

1.2. Indications

"For symptomatic treatment, following on from a previous association of ketoprofen and omeprazole: chronic inflammatory rheumatic conditions, particularly rheumatoid arthritis and ankylosing spondylitis, osteoarthritis.

In the following types of patient:
- patients with a previous history of NSAID-associated gastroduodenal erosions in whom continued treatment with a NSAID is essential;
- patients who are at risk of developing gastroduodenal erosions (particularly those aged > 65 years or with a history of gastroduodenal ulcer) in whom continued treatment with a NSAID is essential.

This fixed-dose combination of ketoprofen and omeprazole should not be used as an initial symptomatic treatment".

1.3. Dosage

"Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Method of administration

Oral use.

Adults and adolescents over the age of 15 years:

This product is not recommended for use in children below 15 years due to a lack of data on tolerance and efficacy in these indications.
The capsule should be swallowed whole with food once daily, preferably in the morning, with a large glass of water.

Dose and administration route

The usual daily dose is 200 mg of ketoprofen and 20 mg omeprazole; however, 100 mg of ketoprofen in combination with 20 mg of omeprazole may be sufficient for some patients.

At-risk populations:

It is recommended that treatment be started with an initial daily dose of 100 mg / 20 mg of XILANIK prolonged-release capsules for such patients.
Use of XILANIK 200 mg / 20 mg prolonged-release capsules must be guided by efficacy and renal safety.

The 100 mg ketoprofen dose should be favoured in elderly patients, those with chronic heart failure and those with renal failure (creatinine clearance 30-50 mL/min) or liver failure."

1.4 Contraindications

- Hypersensitivity to ketoprofen or to omeprazole or to any of the excipients.
- This product contains sucrose and is contraindicated in patients with fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency.
    - Linked to ketoprofen
- Beyond the 24th week of pregnancy (5 months);
- history of asthma induced by administration of ketoprofen or similar acting substances, such as other non-steroidal anti-inflammatory agents (NSAIDs) or acetylsalicylic acid;
- history of haemorrhage or digestive tract perforation during previous NSAID treatment;
- progressive peptic ulcer, history of peptic ulcer or recurrent bleeding (2 or more separate episodes of bleeding or ulceration observed);
- severe hepatic failure;
- severe renal failure;
- severe heart failure;
- gastrointestinal bleeding, cerebrovascular bleeding or other active bleeding.

Note: these contraindications contradict the indication wording in the marketing authorisation for XILANIK.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

M	:	Musculo-skeletal system
M01	:	Antiinflammatory and antirheumatic products
M01A	:	Antiinflammatory and antirheumatic products, non-steroids
M01AE	:	Propionic acid derivatives
M01AE53	:	Ketoprofen, combinations

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

There are no other fixed-dose combinations of a non-steroidal anti-inflammatory (NSAID) and a proton pump inhibitor (PPI) included in the list of medicines reimbursed by National Insurance.

2.3. Medicines with a similar therapeutic aim

- Fixed-dose combination: diclofenac + misoprostol (ARTOTEC), currently being re-assessed by the Transparency Committee.
- All NSAIDs prescribed in combination with misoprostol or PPIs.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The application does not include any clinical studies assessing the efficacy of a fixed-dose combination of ketoprofen and omeprazole (XILANIK) in the indication given in the Marketing Authorisation.

The Marketing Authorisation was granted on the basis of a bibliography-based application alone, which included six clinical studies that evaluated the efficacy of omeprazole in the treatment and prevention of recurrence of gastric and duodenal lesions in patients on NSAID treatment, including ketoprofen [1, 2, 3, 4, 5, 6].

3.2. Adverse effects

The tolerance of XILANIK has not been evaluated specifically.
According to the conclusions of the EMEA 2006 reassessment of the adverse effects of NSAIDs on the cardiovascular and gastrointestinal systems and the skin[7], the benefits of ketoprofen outweigh its risks for daily doses up to a maximum of 200 mg.
The SPC for XILANIK includes special warnings concerning gastrointestinal effects, as follows:
"Omeprazole is an anti-secretory medicine that acts against ulcers. However, because of the possible serious nature of gastrointestinal bleeding, particular caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin. When GI bleeding or ulceration occurs in patients receiving XILANIK, the treatment should be withdrawn. XILANIK modified-release capsules should be given with care and under close monitoring to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated."
However, according to the AFSSAPS 2007 guidelines[8], the following at-risk populations may require NSAID treatment in combination with a PPI:

- persons aged over 65 years
- history of complicated or uncomplicated gastric or duodenal ulcer. In such cases, *Helicobacter pylori* should be tested for and treated.
- combination with anti-platelet therapy, particularly low-dose aspirin and clopidogrel, and/or corticosteroids and/or an anticoagulant (bearing in mind that such combinations should in principle be avoided).

[1] Hawkey C J et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1998; 338 : 727-734.
[2] Yeomans N D et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs. N Engl J Med 1998; 338 : 719-726.
[3] Bianchi Porro M et al. Prevention of gastroduodenal damage with omeprazole in patients receiving continuous NSAIDs treatment. A double blind placebo controlled study. Ital.J Gastroenterol. Hepatol 1998;30:43-47.
[4] Cullen et al. Primary gastroduodenal prophylaxis with omeprazole for non-steroidal anti-inflammatory drug users. Aliment pharmacol Ther 1998; 12: 135-140.
[5] Ekstrom P et al. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. Scand J Gastrol. 1996; 31: 753-758.
[6] Massimo C G et al. Omeprazole 20 or 40 mg for healing gastroduodenal ulcers in patients receiving nonsteroidal anti-inflammatory drugs. Aliment pharmacol Ther 1998; 12: 463-468.
[7] EMEA. Public CHMP assessment report for medicinal products containing non-selective non steroidal anti-inflammatory drugs (NSAIDs) - November 2006.
[8] AFSSAPS. Recommandations de bonne pratique : les antisécrétoires gastriques chez l'adulte. [Good practice guidelines: gastric secretion inhibitors in adults.] November 2007.

3.3. Conclusion

In the absence of studies conducted specifically on XILANIK products, it is not possible to assess the clinical benefit of these products in comparison with separate dosing with a NSAID and a PPI.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Rheumatic conditions can lead to disability and deterioration in quality of life.

XILANIK products are indicated for the conditions stated in the wording of the marketing authorisation, as a continuation treatment following previous combination treatment with ketoprofen and omeprazole for symptomatic treatment of pain and inflammation in at-risk patients for whom NSAID treatment is essential.

In the absence of any studies of their efficacy and tolerance, the efficacy/adverse effect ratio of these products cannot be stated.

Public health benefit

The public health burden caused by chronic inflammatory rheumatic conditions and osteoarthritis, which are chronic and disabling diseases, is considered to be significant. The burden represented by the sub-population of patients who are likely to benefit from this treatment (patients aged over 65 or with a history of gastric or duodenal ulcer) is moderate, because of the more restricted patient numbers involved.

Improvement in management and quality of life of patients with these rheumatic conditions remains a public health need which is included in the list of established priorities (Public Health Law 2004, Plan to improve quality of life of patients with chronic diseases).

However, existing treatments (including flexible combinations of ketoprofen and omeprazole) already help to meet this need.

There is no indication that these fixed-dose combinations have any added benefit (even in terms of increased compliance) over flexible combinations of the two active substances.

As a result, XILANIK is not expected to benefit public health.

In the absence of comparative data, the role of the fixed-dose combination of ketoprofen + omeprazole (XILANIK) in therapeutic strategy in comparison with flexible NSAID + PPI combinations cannot be assessed.

The Transparency Committee also notes that:

- this fixed-dose combination carries the risk of unnecessary use of ketoprofen, which has been shown to have poor digestive tract tolerance.
- making this fixed-dose combination available entails a risk of over-prescription and misuse of PPIs. On the one hand, the ease of use of a dual therapy contained in one capsule carries the risk that prescription of PPIs will shift away from short courses for the treatment of acute conditions, which is contrary to the guidelines on the correct use of PPIs published by HAS[9]. On the other hand, there is the risk that prescription may extend to patients who do not risk developing NSAID-induced gastric and duodenal lesions as defined in the marketing authorisation;
- other treatment options are available.

As a consequence of this, the Transparency Committee considers that the actual clinical benefit of these products, in comparison with the treatments that are already available, is not sufficient to allow it to be reimbursed by National Insurance.

4.2. Transparency Committee recommendations

The Transparency Committee does not recommend inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services.

[9] Bon usage des Médicaments. Les inhibiteurs de la pompe à protons chez l'adulte. Haute Autorité de Santé. Décembre 2009.