HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

3 October 2012

AXORID 100 mg/20 mg, modified-release capsules
B/14 (CIP code: 395 731-3)

AXORID 200 mg/20 mg, modified-release capsules
B/14 (CIP code: 395 734-2)

Applicant: MEDA PHARMA

ketoprofen, omeprazole
ATC code: M01AE53 (NSAID and PPI combination)

List II

Date of Marketing Authorisation: 15 September 2009 (national)

Amendments to the Marketing Authorisation: 16 May 2012 (change to distributor and name of medicinal product)

Reason for request: Inclusion on the list of medicines refundable 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 ingredients

Ketoprofen, omeprazole

1.2. Indications

“Symptomatic treatment, following on from a previous combination of ketoprofen and omeprazole, of:

° chronic inflammatory rheumatic diseases, in particular rheumatoid arthritis and ankylosing spondylitis

° osteoarthritis

In the following patients*:

° **patients who have developed an NSAID-associated gastric or duodenal ulcer and for whom ongoing anti-inflammatory treatment is essential**

° **patients who are at risk of developing an NSAID-associated gastric or duodenal ulcers (in particular age > 65 years, previous history of gastric or duodenal ulcer) and for whom ongoing anti-inflammatory treatment is essential**

The fixed-dose combination of this medicinal product should not be used when establishing 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:
For oral use.
Adults and adolescents over the age of 15 years:
Due to a lack of data in children for these indications, this medicinal product should only be used in adults and adolescents over the age of 15 years.
The capsule should be swallowed whole before a meal, preferably in the morning, with a large glass of water.

Dosage and frequency of administration:
The usual daily dose is 200 mg ketoprofen and 20 mg omeprazole; however, 100 mg ketoprofen combined with 20 mg omeprazole may be sufficient in some patients.

At-risk populations:
In these patients, treatment with this medicinal product should be started at an initial daily dose of 100 mg/20 mg.
Efficacy and renal tolerance should be taken into account when using this medicinal product.
A dose of 100 mg ketoprofen is preferred in elderly patients, patients with chronic heart failure and patients with renal impairment (creatinine clearance 30-50 ml/min) or hepatic impairment.”

1.4. Contraindications

This medicinal product is contraindicated in the following situations:

- pregnancy from 24 weeks (5 months) from the last menstrual period;
- hypersensitivity to ketoprofen or to omeprazole or to any of the excipients;
- history of hypersensitivity reactions such as bronchospasm, asthma, rhinitis, urticaria or other allergic reactions to ketoprofen, acetylsalicylic acid or other NSAIDs. Severe, occasionally fatal anaphylactic reactions have been reported in these patients;
- *gastrointestinal bleeding, cerebrovascular bleeding or other active bleeding;*
- *active peptic ulcer or recurrent bleeding (two or more distinct episodes of bleeding or ulceration documented);*
- severe hepatic failure;
- severe renal failure;
- severe heart failure.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2012)

M: Musculo-skeletal system
M01: Anti-inflammatory and antirheumatic products
M01A: Anti-inflammatory 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 is no other fixed-dose combination of a non-steroidal anti-inflammatory drug (NSAID) and a proton pump inhibitor (PPI) included on the list of medicines refundable by National Health Insurance.

2.3. Medicines with a similar therapeutic aim

- Fixed-dose combination: diclofenac + misoprostol (ARTOTEC), low actual benefit while awaiting further data (opinion of 2 June 2010).
- Any NSAID prescribed concomitantly with misoprostol or a PPI.

3 ANALYSIS OF AVAILABLE DATA

3.1. History of evaluation

Under the name XILANIK, the ketoprofen/omeprazole combination was examined by the Transparency Committee in 2010 in the context of its first application to be included on the list of medicines refundable by National Health Insurance and approved for use by hospitals. The Committee expressed an unfavourable opinion on 5 May 2010, considering that:

"In the absence of any studies of their efficacy and safety, the efficacy/adverse effect ratio of these proprietary medicinal products cannot be stated.
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.[1] 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 benefit of these proprietary medicinal products, in comparison with the treatments that are already available, is not sufficient to allow it to be refundable by National Health Insurance."

Following a change in distributor (now Meda Pharma in place of Pierre Fabre Médicament) and a change in the name of the medicine (AXORID in place of XILANIK), the pharmaceutical company has submitted a new application for inclusion on the list of medicines refundable by National Health Insurance and approved for use by hospitals. In support of this application, there were no clinical studies evaluating the efficacy and safety of the fixed-dose combination of ketoprofen and omeprazole for the indication in the Marketing Authorisation, but there is an observational study aiming to demonstrate a medical need that is not met in actual practice.

3.2. Efficacy and adverse effects

The efficacy and safety of the fixed-dose combination of ketoprofen and omeprazole have not been evaluated.

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

3.3. Observational study (c.f. appendix)

Using data from the LPD database (formerly Thalès), this retrospective observational study analysed how NSAIDs were prescribed by French general practitioners, particularly whether a PPI was prescribed concomitantly, and the persistence of PPI co-prescription in at-risk patients. Patients considered to be at risk were defined as follows:

- aged over 65 years;
- or aged under 65 years with the following risk factors:
    - history of digestive disease or risk factor for ulcer;
    - or diagnosis of cardiovascular disease and/or co-prescription of an anticoagulant or antiplatelet drug;
    - or risk factor for complication in case of bleeding.

Between 1 January and 31 December 2009, an analysis of PPI co-prescription was conducted in patients who had been prescribed an oral NSAID for more than 7 days and who had had a consultation with their doctor in the year preceding the first NSAID prescription in 2009.

Ketoprofen (the NSAID ingredient of AXORID) accounted for 22.6% of NSAIDs prescribed in the study. The mean dose prescribed was 249.9 ± 69.37 mg (median = 300 mg) and the mean duration of prescription was 18.4 ± 19.96 days (median = 10). Note that, following the re-evaluation of the risk/benefit ration of ketoprofen by the EMA, the maximum daily dose should be 200 mg.

Of the 8,178 patients treated with ketoprofen and considered at risk of gastrointestinal events, 4,029 patients (49.3%) had received no concomitant PPI. However, of the 24,232 patients not considered to be at risk of gastrointestinal events, 7,797 (32.2%) had received a co-prescription.

An analysis of PPI co-prescription persistence was also carried out in patients receiving “long-term” NSAID treatment between 2007 and 2009. The long-term nature of this treatment was not defined in terms of days of treatment prescribed, but in terms of the time interval between prescriptions, with at least one repeat prescription every 6 months, i.e. two prescriptions per year.
During the 2 years of follow-up, the mean number of repeat prescriptions for NSAIDs was 9.6 ± 4.57 (median = 8) with a mean prescription duration of 45.5 ± 32.61 days (median = 30 days).
PPI co-prescription persistence at 2 years was 68.3% [66.1; 70.4] for NSAIDs as a whole, and 70.2% [64.5; 75.1] for ketoprofen.
Multivariate analysis demonstrated that in patients treated with ketoprofen, a change in the NSAID prescribed was associated with the PPI co-prescription being stopped. For NSAIDs as a whole, in addition to this factor, the occurrence of a gastrointestinal adverse event was also associated with the PPI treatment being stopped (HR = 1.33 [1.06; 1.66]).

The results of this study do not allow the impact of PPI co-prescription and PPI co-prescription persistence to be evaluated in terms of any reduction in NSAID-associated gastrointestinal events, because no information was provided about the chronology between the gastrointestinal event occurring and the PPI co-prescription being stopped, and because recurrent gastrointestinal events were not taken into account.

In sum, this study does not provide any information about compliance in at-risk patients who are prescribed a PPI together with an NSAID, nor about the impact of this co-prescription on the occurrence of gastrointestinal adverse events.

3.4. Further information

Marketing authorisation
This fixed-dose combination has obtained Marketing Authorisation in six European countries in addition to France: Spain, the UK, Italy, Poland, Portugal and Romania.

Reimbursement
This fixed-dose combination is currently covered by National Health Insurance in three European countries: the UK, Italy and Romania.

Post-inclusion study
The pharmaceutical company intends to conduct a post-inclusion study to confirm that AXORID is being used appropriately, in particular in the at-risk patients defined by the guidelines.

3.5. Conclusion

In support of its application, the pharmaceutical company has not submitted any clinical study that has evaluated the efficacy and safety of the fixed-dose combination of ketoprofen and omeprazole for the indication in the Marketing Authorisation; the application is based solely on a retrospective observational study that aims to describe how NSAIDs are prescribed by French general practitioners and more particularly their concomitant prescription with a PPI.

Given the lack of any clinical study conducted specifically with the fixed-dose combination of ketoprofen and omeprazole (AXORID), or of any comparative study versus a free combination of ketoprofen and omeprazole or other NSAID + PPI combinations, it is not possible to assess the intrinsic clinical benefit of AXORID and its benefit in comparison to the separate administration of an NSAID and a PPI.

Finally, there is no justification for the choice of ketoprofen as the NSAID in this combination, in particular in terms of gastrointestinal safety.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Rheumatic diseases can lead to disability and cause patients' quality of life to deteriorate. However, treating these conditions with NSAIDs can have harmful gastrointestinal consequences, which account for a significant proportion of drug iatrogenesis.

According to the wording of their Marketing Authorisation, the AXORID products are indicated "following on from a previous combination of ketoprofen and omeprazole" in the context of symptomatic treatment of pain and inflammation in at-risk patients for whom NSAID treatment is essential.

Given the lack of any clinical studies evaluating their efficacy and safety, the efficacy/adverse effects ratio of these products cannot be specified.

> Public health benefit:
> The public health burden of chronic inflammatory rheumatic diseases and osteoarthritis, which are chronic and disabling diseases, is considered to be significant. The public health burden in the subpopulation likely to benefit from this treatment (patients aged over 65 years or with a history of gastric or duodenal ulcer) is moderate, given the smaller number of patients concerned.
> Improving the management of patients with these rheumatic diseases and their quality of life is a public health need which is an established priority (French Public Health Law of 2004, Plan for improving the quality of life of patients with chronic diseases).
> However, existing treatments (including free 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 free combinations of the two active substances.
> Consequently, the proprietary medicinal product AXORID is not expected to benefit public health.

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

There are many treatment alternatives (free combinations of an NSAID and a PPI or misoprostol), some of which are better tolerated by the gastrointestinal tract and have better justification for the choice of NSAID.

Consequently, the Transparency Committee considers that the actual benefit of these proprietary medicinal products, in comparison with the treatments that are already available, is not sufficient to justify reimbursement by National Health Insurance.

4.2. Improvement in actual benefit (IAB)

Not applicable

4.3. Therapeutic use

Not applicable

4.4. Target population

Not applicable

4.5. Transparency Committee recommendations

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

AXORID
LPD-CEGEDIM Observational Study
A study of how NSAIDs are prescribed in current practice and of PPI co-prescription persistence in at-risk patients on long-term NSAID treatment

Objectives

The study of how NSAIDs are prescribed (Analysis 1) has the following objectives:

- To characterise the management of patients treated with NSAIDs, and more specifically with ketoprofen, particularly in terms of indication and dosage, in current practice.
- To analyse PPI co-prescription and how this evolves as and when NSAID prescriptions are renewed.
- To study the patient profile.

The study of PPI co-prescription persistence in at-risk patients on long-term NSAID treatment (Analysis 2) has the following objectives:

- To study the profile of at-risk patients.
- To study the persistence of PPI co-prescription when the NSAID treatment is renewed; patients are defined as persistent if they have a concomitant PPI prescription for each NSAID repeat prescription.
- To analyse the factors associated with non-continuation of PPI treatment when the NSAID prescription is renewed.
- To study the coverage rate of NSAID treatment by a PPI prescription.
- To study the occurrence of new gastrointestinal events in at-risk patients.

Population

Study of the data from 1,200 general practitioners in the LPD database (formerly Thalès). In 2009, the sample of GPs in the LPD database was representative of French GPs according to the following criteria: age, gender, region of practice and sector of activity.

Inclusion criteria for the study of how NSAIDs are prescribed

- Patients who were treated for more than 7 days with an oral NSAID in 2009;
- Patients followed up regularly by their GP (who had a consultation with their GP in the year preceding the first prescription of an NSAID in 2009).

The date of inclusion corresponds to the first date of prescription in 2009 of an oral NSAID treatment for more than 7 days.

Inclusion criteria for the study of PPI co-prescription persistence in at-risk patients on long-term NSAID treatment

- . Patients considered to be at risk, defined as follows:
  - aged over 65 years;
  - or aged under 65 years with at least one of the following risk factors:
    - history of digestive disease or risk factor for ulcer;
    - or diagnosis of cardiovascular disease and/or co-prescription of an anticoagulant or antiplatelet drug;
    - or risk factor for complication in case of bleeding.
- Patients who were treated for more than 7 days with an oral NSAID in 2007;
- Patients followed up regularly by their GP (who had a consultation with their GP in the year preceding the first prescription of an NSAID in 2007);
- Patients who were receiving a concomitant PPI treatment with their NSAID treatment on inclusion;

- Patients whose NSAID treatment was renewed at least once during the follow-up period;
- Patients who received NSAID prescriptions in the 2007-2009 period within a maximum period of 180 days after the date of their previous prescription (selection criteria for patients on long-term NSAID treatment).
  (NB: long-term treatment defined by time period between prescriptions and not in terms of the number of days of treatment prescribed.)

The date of inclusion corresponds to the first date of prescription in 2007 of an oral NSAID treatment for more than 7 days.

Periods of analysis

The data available covered the period of 1 January 2009 to 31 December 2009 for the study of how NSAIDs are prescribed (Analysis 1) and the period of 1 January 2007 to 31 December 2009 for the study of persistence at 2 years (Analysis 2).
Some data, such as the disease profile, were sought in the history of patients' medical files.

Evaluation criteria for persistence

Patients were defined as persistent if they had a concomitant PPI prescription for each NSAID repeat prescription.
PPI treatment was defined as concomitant when there was an overlap between NSAID and PPI prescriptions (rabeprazole was excluded because it does not have the indication "prevention of NSAID-induced lesions in at-risk patients"). The prescription of misoprostol was not included in the study.

Results

Study of how NSAIDs are prescribed (Analysis 1)

A total of 143,866 patients who had received at least one NSAID prescription for a duration of more than 7 days and been followed up regularly by their GP were identified in the LPD database for 2009. Among these, 18.1% of patients were aged over 65 (data missing in 249 patients). The mean number of NSAID prescriptions (oral form) in 2009 was 1.9 ± 1.4 prescriptions (median = 1). Rheumatic diseases were the reason for 60% of NSAID prescriptions. 58.8% of patients considered as at risk (age > 65 years or risk of gastrointestinal complications) had no PPI co-prescription. A concomitant PPI prescription was found in 23.1% of patients not identified as at risk.
Ketoprofen (the NSAID ingredient of AXORID) accounted for 22.6% of NSAIDs prescribed in the study. The mean dose of ketoprofen prescribed was 249.9 ± 69.37 mg (median = 300) and the mean duration of prescription was 18.4 ± 19.96 days (median = 10). Among patients treated with ketoprofen, 49.3% of at-risk patients (age > 65 years or risk of gastrointestinal complications) had no PPI co-prescription and 32.2% of patients not identified as at-risk received a PPI co-prescription.
The analysis did not take into account whether treatment was long-term or brief.

Study of PPI co-prescription persistence in at-risk patients on long-term NSAID treatment (Analysis 2)

In the 2007-2009 period, 1,856 patients identified as at risk of gastrointestinal complications (of whom 74.4% were aged over 65) received long-term NSAID treatment and had at least one concomitant PPI prescription in 2007.
The main NSAIDs prescribed on inclusion were diclofenac (24.5%), ketoprofen (15.2%, 285 patients), piroxicam (14.2%) and celecoxib (10.1%).

During the 2 years of follow-up, the mean number of repeat prescriptions for NSAIDs was 9.6 ± 4.57 (median = 8) with a mean prescription duration of 45.5 ± 32.61 days (median = 30 days). PPI co-prescription persistence at 2 years was 68.3% [66.1; 70.4] for NSAIDs as a whole. For patients treated with ketoprofen, PPI co-prescription persistence at 2 years was 70.2% [64.4; 75.1]. Of the 85 patients no longer receiving concomitant PPI

prescriptions at 2 years, almost a third (31.8%) had had at least one change in the NSAID prescribed during the 2 years.

Multivariate analysis was performed and demonstrated that the following factors influenced the stopping of PPI co-prescription:

- change in NSAID drug (HR = 2.01 [1.69; 2.39])
- gastric symptoms or adverse events were associated with stopping the PPI (HR = 1.33 [1.06; 1.66])
- gender (PPI stopped more frequently in women, HR = 1.26 [1.06; 1.50])
- number of co-prescriptions (HR = 0.94 [0.91; 0.96])

In the population of patients treated with ketoprofen on inclusion, only a change in NSAID was associated with stopping PPI co-prescription (HR = 2.76 [1.74; 4.37]).

The following analyses were conducted on all at-risk patients on any long-term NSAID treatment (not just those treated with ketoprofen). Among the 588 at-risk patients whose PPI co-prescription was stopped, reintroduction of the PPI within 6 months of stopping was observed in 50% of patients. In 45 patients (7.7%), the reason for reintroducing the PPI was the onset of gastrointestinal adverse events.

An analysis of the occurrence of gastrointestinal adverse events in at-risk patients according to PPI prescription persistence was performed. However, only events that occurred during the follow-up period and were worded differently to the patient's previous gastrointestinal events were taken into account, thus excluding recurrences. Furthermore, the chronology between the occurrence of the gastrointestinal event and the stopping of PPI co-prescription was not taken into account and the definition of persistence seems to have been changed (different numbers to the previous analyses). The results of this analysis therefore cannot be interpreted, especially as the previous analyses identified that the occurrence of gastric symptoms or adverse events was a factor associated with the stopping of PPI co-prescription.

Conclusion

This study describes how NSAIDs are prescribed (with or without PPIs) by general practitioners and evaluates PPI co-prescription persistence in at-risk patients on "long-term" NSAID treatment. Long-term NSAID treatment was defined by prescription frequency (at least once every 6 months over a period of 2 years) without taking into account the number of days of treatment prescribed during that period.

Among the 8,178 patients treated with ketoprofen and considered at risk of a gastrointestinal event (age > 65 years, history of digestive disease or of risk factors for ulcer, co-prescription of an anticoagulant or antiplatelet drug), 4,029 (49.3%) received no concomitant PPI. However, of the 24,288 patients not considered to be at risk of gastrointestinal events, 7,797 (32.2%) received a co-prescription.

The impact of PPI co-prescription persistence on the occurrence of gastrointestinal events cannot be evaluated from this study's data because the chronology between occurrence of the gastrointestinal event and stopping of PPI co-prescription, as well as recurrences of gastrointestinal events, were not taken into account.

In sum, this study does not provide any information about compliance in at-risk patients who are prescribed a PPI together with an NSAID, nor about its impact on the occurrence of gastrointestinal adverse events.