



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

1 April 2009

PROXALYOC 10 mg, oral lyophilisate
Box of 30 (CIP: 343 619-8)

PROXALYOC 20 mg, oral lyophilisate
Box of 10 (CIP: 343 620-6)

Applicant: CEPHALON

Piroxicam
ATC: M01AC01

List I

Date of Marketing Authorisation:

- PROXALYOC 10 mg and PROXALYOC 20 mg: 24 July 1997
- Date of last amendment: 21 May 2008 (sections: Therapeutic indications, Posology and method of administration, Contraindications, Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction and Undesirable effects).

Reason for request: Reassessment of the actual benefit of piroxicam-based proprietary medicinal products for systemic use under article R.163-21 of the Social Security Code. This reassessment follows the EMEA arbitration procedure on piroxicam-based proprietary medicinal products.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

piroxicam

1.2. Indications

previous text

"The indications are related to the anti-inflammatory action of piroxicam, the severity of side effects caused by the medicine, and its place in the range of anti-inflammatory medicines currently available.

The indications in adults and children aged 15 years and over are restricted to :

- long-term symptomatic therapy:
 - chronic inflammatory rheumatic diseases, particularly rheumatoid arthritis, ankylosing spondylitis (or related syndromes, such as Reiter's syndrome and psoriatic arthritis),
 - certain forms of painful and incapacitating osteoarthritis.
- short-term symptomatic treatment of acute episodes of:
 - non-articular rheumatic conditions such as scapulohumeral periarthritis, tendinitis, bursitis,
 - acute post-traumatic disorders of the musculoskeletal system,
 - microcrystalline arthritis,
 - osteoarthritis,
 - ."radiculalgia

New text:

"Piroxicam is indicated in the symptomatic treatment of osteoarthritis, rheumatoid polyarthritis and ankylosing spondylitis. In view of its safety profile (see sections 4.2, 4.3 and 4.4 of the SPC), piroxicam must not be used as first-line treatment where NSAID treatment is indicated.

The decision to prescribe a proprietary medicinal product containing piroxicam must be based on an assessment of all the risks to which the patient in question may be exposed (see sections 4.3 and 4.4 of the SPC)."

1.3. Dosage

The prescription of piroxicam-containing medicines should be initiated by physicians with experience in the diagnostic evaluation and treatment of patients with inflammatory or degenerative rheumatic diseases.

The medicine should only be used in adults and children aged 15 years and over.

The maximum recommended daily dose is 20 mg.

The occurrence of adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. The benefit and tolerability of treatment should be reviewed within 14 days.

Continued treatment, if considered necessary, should be accompanied by frequent review.

Given that piroxicam has been shown to be associated with an increased risk of gastrointestinal complications, the possible need for combination therapy with gastroprotective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered, in particular for elderly patients.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

M	:	Musculo-skeletal system
M01	:	Antiinflammatory and antirheumatic products
M01A	:	Antiinflammatory and antirheumatic products, non-steroids
M01AC	:	oxicams
M01AC01	:	piroxicam

2.2. Medicinal products in the same therapeutic category

2.2.1. Similar medicines in the same therapeutic category

These are other medicines containing piroxicam for systemic use and their generic equivalents, the indications for which are restricted to treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylosis as second line therapy when an NSAID is indicated:

- BREXIN 20 mg, scored tablets and effervescent tablet
- CYCLADOL 20 mg, scored tablets and effervescent tablet
- FELDENE 10 mg, capsule
- FELDENE 20 mg, capsule, dispersible tablet and suppositories
- FELDENE 20 mg/1 mL, solution for injection

2.2.2. Medicines in the same therapeutic category that are not strictly similar

Other medicinal products, and their generic equivalents, in the category of oxicams for systemic use:

- meloxicam: MOBIC 7.5 and 15 mg tablets, 7.5 and 15 mg capsules, 7.5 mg/mL oral suspension, 7.5 and 15 mg suppositories and 15 mg/1.5 mL solution for injection
- tenoxicam: TILCOTIL 20 mg tablets, effervescent tablet, suppository and freeze-dried powder and solution for parenteral use

2.3. Medicinal products with the same therapeutic aim

These are other NSAIDs (indoles and their derivatives, aryl-carboxylic derivatives, fenamates, pyrazoles, selective COX-2 inhibitors) and steroidal anti-inflammatory drugs.

3 ANALYSIS OF AVAILABLE DATA

Reminder of the background:

Following an application of the European Commission, the Committee for Medicinal Products for Human Use (CHMP) re-examined the tolerance data for nonselective NSAIDs. During that re-examination, the CHMP produced recommendations on common amendments to the summary of product characteristics for nonselective NSAIDs and concluded there was a need to make an in-depth evaluation of the risk/benefit ratio for certain NSAIDs, including piroxicam. That evaluation, which was completed in June 2006, revealed a potentially increased risk of gastrointestinal and cutaneous reactions (including a potentially fatal bullous eruption) with piroxicam as compared to other nonselective NSAIDs. The European Commission believed that public health interests necessitated a new evaluation of the risk/benefit ratio for piroxicam and asked the CHMP to produce an opinion on the maintenance, amendment, suspension or withdrawal of marketing authorisations for medicinal products containing piroxicam.

On 21 June 2007, the CHMP concluded that systemic formulations of piroxicam were associated with “an increased risk of severe gastrointestinal toxicity by comparison with other NSAIDs, and an increased risk of severe cutaneous reactions compared to other non-oxicam-derivatived NSAIDs”. However, the CHMP thought that the risk/benefit ratio for piroxicam remained positive in the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, subject to amendment of the conditions for use of these medicines. For the treatment of other acute-phase conditions, the risk/benefit ratio was regarded as negative because of the long half-life (50 hours) of piroxicam and its tolerance profile.

As regards topical formulations of piroxicam, no restriction was considered necessary because systemic exposure was less than with formulations for systemic use.

The amendments that have been made to the summary of product characteristics for medicines containing piroxicam are as follows:

- Therapeutic indication: piroxicam is for use only in the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. However, in these indications, it must not be used as a first-line treatment when an NSAID is indicated.
- As with any NSAID, treatment must be administered in the lowest dose (not more than 20 mg/day) and for the shortest period possible.
- The prescription must be initiated by a physician with experience in the monitoring of patients with degenerative or inflammatory rheumatic disorders. In all cases, the treatment must be reassessed at the end of 14 days treatment.
- Physicians must consider prescribing piroxicam with a gastroprotective medicine (such as misoprostol or a proton pump inhibitor), particularly in elderly patients.
- Medicines containing piroxicam must not be prescribed in patients with a history of gastrointestinal haemorrhages, or cutaneous reactions with any other medicine.
- Medicines containing piroxicam must not be prescribed in combination with another NSAID or with an anticoagulant.

The data presented below are the data which the CHMP used in the arbitration procedure which led to the re-evaluation of the risk/benefit ratio for piroxicam-based medicines for systemic use (opinion of 3 July 2007).

3.1. Efficacy

Gaffney (1998)¹ :

A meta-analysis of 38 published, randomised clinical studies which evaluated the efficacy and gastrointestinal tolerance of piroxicam 20 mg in comparison with various NSAIDs (naproxen, diclofenac, nabumetone, ibuprofen, tenoxicam, indomethacin, etodolac and oxaprozin) in patients with chronic (osteoarthritis and rheumatoid arthritis) and acute disorders.

Of the 11,705 patients included in the analysis of efficacy, 9,041 were treated for a chronic condition, 2,599 of whom received piroxicam, and 2,664 for an acute condition, out of which 1,333 patients received piroxicam.

In the indications osteoarthritis and rheumatoid arthritis, the response rates (unspecified endpoint) were 53.3% with piroxicam 20 mg and 54.6% with the other comparators (RR = 0.97, nonsignificant difference).

These results should be interpreted with caution, since this study was not the subject of a publication but merely a congress poster.

3.2. events

3.2.1. Gastrointestinal tolerance

- **Data from clinical studies**

Three meta-analyses (2 of which have not been published but were the subject of a communication at a conference) and 1 combined analysis of studies were used by the CHMP (see Table 1 in appendix).

Richy (2004)² :

Thirty two randomised, controlled clinical studies comparing different NSAIDs in a placebo group or a group of patients who were not exposed to NSAIDs, were used in this meta-analysis. The results showed an increased risk of the occurrence of gastrointestinal complications for all NSAIDs, compared to that of the placebo control group:

- indomethacin: RR = 2.25; 95% CI = [1.00; 5.07]
- naproxen: RR = 1.83; 95% CI = [1.25; 2.68]
- diclofenac: RR = 1.73; 95% CI = [1.21; 2.46]
- piroxicam: RR = 1.66; 95% CI = [1.14; 2.44]
- **tenoxicam: RR = 1.43; 95% CI = [0.40; 5.14]**
- meloxicam: RR = 1.24; 95% CI = [1.00; 5.07]
- ibuprofen: RR = 1.19; 95% CI = [1.00; 5.07]

This study does not show any excess risk of gastrointestinal complications with piroxicam as compared to other NSAIDs. It should be noted that the populations included for the various NSAIDs were variable, ranging from 284 patients (3 studies) for piroxicam to 1495 patients for meloxicam.

¹ Results presented in poster form: Gaffney M, Curiale C and Cimmino AA. Piroxicam risk/benefit ratio: a meta-analysis of 38 published papers. Meeting of the OARS, October 15-17, 1998, Florence, Italy.

² Richy F et al. Time dependant risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use : a consensus statement using a meta-analytic approach, Annals of the rheumatic diseases, 2004, 63: 759-766

Singh (2004)³ :

The results of 28 clinical studies⁴, for which the principal criteria was to include a meloxicam group were used in this study to calculate the cumulative risk of serious gastrointestinal adverse events for a treatment period of up to 2 months. This risk was greater with piroxicam than with meloxicam 15 mg/day (0.9% versus 0.2%, $p = 0.03$). No statistically significant difference was seen between piroxicam and diclofenac on the one hand and piroxicam and naproxen on the other.

These results must be interpreted with caution since this is a combined analysis of several studies which does not satisfy the methodological requirements of a meta-analysis of studies analysing survival (in particular, no description of the individual studies, no test of heterogeneity of the results, no analysis of selection bias, no account taken of the multiplicity of analyses and the increase in significance level).

Gaffney (1998)⁵ :

In this meta-analysis, described above, which included 38 studies⁵ (15,208 patients analysed for tolerance), no statistically significant difference was found between piroxicam and its NSAID comparators (NSAID type not specified) in the occurrence of gastrointestinal adverse events in either chronic or acute conditions. The incidence of cases of gastrointestinal adverse events such as haemorrhage or ulcer was too low to allow a statistical analysis to be made of the difference between piroxicam and the other NSAIDs (15/3,020 with piroxicam and 20/7,221 with the comparators). No adverse effect such as haemorrhage/ulcer was observed in patients with acute conditions.

These results must be interpreted with caution since no detail is available of this study, which was presented at a congress.

Richy (2007)⁶ :

This meta-analysis included 75 clinical studies⁵, 45 of which involved the analysis of major gastrointestinal adverse effects under piroxicam versus other NSAIDs. No statistically significant difference was found between piroxicam and the other NSAIDs as regards the risk of occurrence of major gastrointestinal events (combined OR = 1.33; 95% CI = [0.96; 1.84]).

These results must be interpreted with caution, since this study was not the subject of a publication but merely a communication at a congress.

- **Data from epidemiological studies**

The evaluation of epidemiological data on the risk of gastrointestinal complications is based mainly on the meta-analysis by Hernandez-Diaz (2000)⁷ (see Table 2 in appendix).

Hernandez-Diaz (2000) :

This meta-analysis of 15 case-control studies and 3 observational studies showed an increased risk of severe upper gastrointestinal complications with piroxicam and other NSAIDs as compared to patients who were not NSAID users. No statistical analysis was made of comparisons between piroxicam and the other NSAIDs; however, it is seen that the

³ Singh S et al. Risk of serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam. The American journal of medicine, 2004, 117: 100-106

⁴ The randomised and controlled nature of the studies has not been specified.

⁵ Gaffney M et al. Piroxicam risk/benefit ratio: a meta-analysis of 38 published papers. Meeting of the OARS, 1998, Florence, Italy (poster)

⁶ Richy F et al. Meta-analysis of 75 RCT with Piroxicam 2007, (ECCE07: 7th European Congress on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis), <http://www.ecce07.org/knee.html>

⁷ Hernandez-Diaz S et al. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation. Archives of internal medicine, 2000, 160:2093-2099

lower limit of the 95% confidence interval for the relative risk of piroxicam vs patients who were not NSAID users was greater than the upper limit of that for other NSAIDs except ketoprofen:

- **piroxicam:** RR = 6.3; 95% CI = [5.5; 7.2]
- ketoprofen: RR = 4.6; 95% CI = [3.3; 6.4]
- indomethacin: RR = 4.6; 95% CI = [3.8; 5.5]
- naproxen: RR = 4.0; 95% CI = [3.5; 4.6]
- sulindac: RR = 3.8; 95% CI = [3.6; 4.1]
- diclofenac: RR = 3.6; 95% CI = [2.8; 4.7]
- ibuprofen: RR = 3.3; 95% CI = [2.8; 3.9]

Five other studies that are not included in these meta-analyses were published after 2001 (see table 3 in appendix): 2 cohort studies, Gallerani (2004)⁸ and Mellemkjaer (2002)⁹ and 3 case-control studies, Laporte (2004)¹⁰, Lanass (2003)¹¹ and Lanass (2006)¹². A similar result was observed in these studies, with a risk of haemorrhagic upper gastrointestinal complications which is larger with piroxicam than with other NSAIDs except ketoprofen in 1 study and ketorolac in 2 studies. In these studies, the odds ratio for the risk with piroxicam was 4.76 (95% C = [2.98; 7.60]), 5.00 (95% CI = [3.3; 7.2]), 15.5 (95% CI = [10.0; 24.2]), 18.5 (95% CI = [9.2; 36.9]) and 12.6 (95% CI = [7.8; 20.3]).

3.2.2. Cutaneous effects

The evaluation of the cutaneous tolerance of piroxicam is based on 2 case-control studies: Roujeau (1993)¹³ and Mockenhaupt (2003)¹⁴. These studies showed that oxicam derivative NSAIDs including piroxicam were associated with an increased risk of serious cutaneous reactions (mainly Stevens-Johnson syndrome, toxic epidermal necrolysis, or Lyell's syndrome, and erythema multiforme). However, among the oxicams, the risk is greatest with tenoxicam.

In the Mockenhaupt study, which is an update of the Roujeau study (1993), the relative risks observed are as follows:

- oxicams: RR = 34; 95% CI = [11; 105]
- tenoxicam: RR = 43; 95% CI = [12; 145]
- **piroxicam:** **RR = 20; 95% CI = [6; 67]**
- propionic acid derivatives: adjusted RR = 1.9; 95% CI = [0.7; 5.0]
- diclofenac: adjusted RR = 4.1; 95% CI = [1.5; 11.0]

These results must be interpreted with caution given the rarity of the cases, which is reflected in the very broad confidence intervals.

⁸ Gallerani M et al. Risk of hospitalization for upper gastrointestinal tract bleeding. Journal of Clinical Epidemiology, 2004, 57:103-110

⁹ Mellemkjaer L et al. Upper gastrointestinal bleeding among users of NSAIDs : a population-based cohort study in Denmark. British journal of clinical pharmacology, 2002, 53 173-181

¹⁰ Laporte JR et al. Upper gastrointestinal bleeding associated with the use of NSAIDs : newer versus older agents. Drug Safety, 2004, 27 (6):411-420

¹¹ Lanass A et al. Risk of upper gastrointestinal bleeding associated with non-aspirin cardiovascular drugs, analgesics and nonsteroidal anti-inflammatory drugs. European Journal of Gastroenterology and Hepatology, 2003, 15:173-178

¹² Lanass A et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut, 2006, 55:1731-1738

¹³ Roujeau JC et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. The new England journal of medicine, 1995, 333:1600-7

¹⁴ Mockenhaupt M. The risk of Stevens - Johnson syndrome and Toxic Epidermal Necrolysis associated with nonsteroidal antiinflammatory Drugs: a multinational perspective. The journal of rheumatology, 2003, 30:2234-40

This study also showed that the risk of severe cutaneous reactions with NSAIDs is greater in the first 2 months of treatment:

- | | |
|---|------------------------------|
| - oxicams $\leq$ 2 months: | RR = 72; 95% CI = [25; 209] |
| - oxicams $>$ 2 months: | RR = 0; 95% CI = [0; 47] |
| - propionic acid derivatives $\leq$ 2 months: | RR = 5.4; 95% CI = [2.4; 12] |
| - propionic acid derivatives $>$ 2 months: | RR = 2.4; 95% CI = [0.4; 13] |

The CHMP considered that the risk of serious cutaneous reactions associated with piroxicam, although not very large in absolute terms, could not be dismissed, given the severity of the conditions considered and the risk of a fatal outcome (mortality rate of about 40% for the severe forms).

3.2.3. Cardiovascular effects

The evaluation of the cardiovascular tolerance of piroxicam is based essentially on the meta-analysis by McGettingan (2006)¹⁵ which included 23 observational studies (1985-2006), of which 17 were case-control studies (86,193 cases and at least 528,000 controls) and 6 observational studies (75,520 patients under coxib, 375,619 under non-coxib NSAIDs and 594,720 not exposed to NSAIDs).

The aim of this meta-analysis was to compare the risks of severe cardiovascular complications of the different NSAIDs.

In the case-control studies, the patients had had an infarction or sudden cardiovascular death. In one study, cases of unstable angina were also included. In the observational studies, the main endpoint studied was infarction and sudden cardiovascular death.

There was not seen to be any excess risk of cardiovascular complications with piroxicam as compared to other NSAIDs.

3.2.4. Pharmacovigilance data

The pharmacovigilance data for piroxicam show that severe gastrointestinal adverse events occur at the recommended dose (94% of cases) and after several weeks of treatment (59%).

As regards spontaneous reports on the risk of serious cutaneous reactions, most of the cases recorded also occurred at the recommended doses (20 mg) and in the 14 days following the start of treatment (68% of cases).

The CHMP stresses that although there may be a bias in favour of declaring events occurring a short time after taking piroxicam, the data suggest that this risk of short-term serious gastrointestinal and cutaneous complications must not be neglected.

3.3. **Conclusions**

A meta-analysis of 38 randomised clinical studies confirmed that the level of efficacy of piroxicam is comparable to that of other NSAIDs.

The results of epidemiological studies (observational studies and case-control studies) suggest an increased risk of serious gastrointestinal complications (haemorrhages, ulcers, perforations) and serious cutaneous reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme) with piroxicam compared to other NSAIDs. The

¹⁵ McGettingan P. et al. Cardiovascular risk and inhibition of cyclooxygenase : a systematic review of the observational studies of selective and non selective inhibitors of cyclooxygenase. JAMA, 2006;vol 296, n°13: 1633-1643

overwhelming majority of these serious adverse effects occur at the recommended doses and in the first weeks following treatment initiation.

The serious cutaneous adverse effects are rare in absolute terms but this risk must not be dismissed, given that 40% of cases have a fatal outcome. This increased risk is shared with the other active ingredients in the oxicam class; tenoxicam seems to be associated with the greatest risk.

The epidemiological data did not lead the CHMP to change its opinion on the cardiovascular tolerance of NSAIDs and piroxicam does not seem to be associated with any greater cardiovascular risk than the other NSAIDs.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Re-evaluation of actual benefit

Rheumatoid arthritis is a chronic inflammatory form of rheumatism which is potentially serious and disabling and most often affects women.

Ankylosing spondylitis is a chronic inflammatory disease which mainly affects the vertebral column and the sacroiliac joints (axial form) and the peripheral entheses (especially the heel). The disease, which generally starts between the ages of 15 and 40 years, affects men three times more often than women.

Osteoarthritis is an articular disease the prevalence of which increases with age. It can cause pain and is characterized by potential progression towards handicap and/or a marked deterioration in the quality of life. The disabling forms, particularly of the hip and the knee, require surgical treatment.

These medicinal products are intended as symptomatic treatment.

Public health benefit:

The public health burden of osteoarthritis (disabling osteoarthritis of the knee and the hip) is great. That caused by rheumatoid arthritis and by ankylosing spondylitis is important .

For most patients with osteoarthritis, rheumatoid arthritis or ankylosing spondylitis, the therapeutic needs are theoretically covered by the use of other NSAIDs.

In view of the data available in the therapeutic indications, and in particular due to the risk of adverse effects, there is no evidence that PROXALYOC will have a positive impact on morbidity and mortality.

Consequently, it is not expected that PROXALYOC will benefit public health.

The adverse effects linked to piroxicam are the classic adverse effects of NSAIDs: gastrointestinal disorders, hypersensitivity reactions (dermatological, respiratory and general), effects on the central nervous system, mucocutaneous reactions. However, the epidemiological data available have shown an increased risk of serious gastrointestinal adverse effects (ulcers with haemorrhagic complications, perforations) and serious cutaneous effects (toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme) with piroxicam as compared to other NSAIDs.

The efficacy/adverse effects ratio is moderate in rheumatoid arthritis and ankylosing spondylitis.

The efficacy/adverse effects ratio is low in symptomatic arthrosis of the hip and the knee.

These are second-line treatments when an NSAID is indicated.

The actual benefit of PROXALYOC medicinal products is moderate, in second-line treatment when an NSAID is indicated, in rheumatoid arthritis, ankylosing spondylitis and symptomatic osteoarthritis of the hip and the knee. It is insufficient in other types of osteoarthritis.

4.2. Therapeutic use

Rheumatoid arthritis:

The treatment of rheumatoid arthritis is intended to relieve pain, alleviate functional handicap and preserve joint function.

Drug treatment consists of immediate-acting symptomatic treatment (NSAIDs, low-dose corticosteroids and/or analgesics) and a disease-modifying therapy which is intended to put the disease into remission and slow down joint destruction. Anti-TNFs are directed towards forms which do not respond to the classic disease-modifying treatments, including methotrexate, and the severe, active and progressive forms of the disease.

Ankylosing spondylitis:

The aim of treatment is mainly to relieve pain, alleviate functional handicap and prevent stiffening and deformation.

NSAIDs are used in first-line therapy. Disease-modifying medicines are useful in forms where peripheral joints are affected.

Rehabilitation is intended to prevent ankylosis (joint motion and chest expansion) and deformation.

Anti-TNFs (infliximab, etanercept) are indicated in patients with severe forms that are insufficiently controlled by NSAIDs prescribed in the maximum tolerated dose.

Osteoarthritis of the hip and knee:

The medical management of patients with osteoarthritis is based on:

- non-drug treatments: losing excess weight, functional rehabilitation, use of sticks, etc.
- drug treatments (including analgesics) when the condition is painful.

Paracetamol is the analgesic of first choice and, if effective, the medicine to be preferred in the long term.

NSAIDs are used as second-line therapy (if paracetamol fails), for the minimum period necessary and at the lowest effective dosage.

4.3. Recommendations of the Transparency Committee

The Transparency Committee recommends upholding 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 in the following indications and at the dosages in the Marketing Authorisation: symptomatic treatment of rheumatoid arthritis, ankylosing spondylitis and disabling symptomatic osteoarthritis of the hip and the knee.

4.3.1. Packaging: Appropriate for the prescription and supply conditions

4.3.2. Reimbursement rate: 35%

ANNEXES

Table 1: Summary of meta-analyses of clinical trials studying the gastrointestinal side-effects of piroxicam

Ref	Type of study:	Effect studied	Comparators	Results																												
Richy (2004)	- Meta-analysis of 32 randomised controlled clinical trials and 13 controlled observational studies (1985-2003) - 3 randomised clinical trials evaluating piroxicam versus placebo or non-users of NSAIDs (284 patients) - Aim: to evaluate the risk of GI complications of the principal NSAIDs, notably in relation to duration of exposure.	→<u>Depending on the study, two types of endpoint:</u> - minor GI event (abdominal pain, nausea, constipation, diarrhoea or dyspepsia). - major GI event (gastric, duodenal or intestinal ulcer, bleeding, perforation, drug-related admission to hospital or death). →<u>Endpoints of the 3 trials of piroxicam:</u> minor (29 patients), major (229 patients) or severe (26 patients) GI complication	indomethacin, naproxen, diclofenac, piroxicam, tenoxicam, meloxicam, ibuprofen Comparison with inactive control: placebo or group not exposed to NSAIDs	Risk of GI complication in patients taking NSAIDs compared with patients not exposed to NSAIDs or on placebo <table><tr><th colspan="2">Combined RR from clinical trials (CI95%)</th></tr><tr><td>Indomethacin (n=1 357)</td><td>RR = 2.25 [1.00; 5.07]</td></tr><tr><td>Naproxen (n=792)</td><td>RR = 1.83 [1.25; 2.68]</td></tr><tr><td>Diclofenac (n=1132)</td><td>RR = 1.73 [1.21; 2.46]</td></tr><tr><td>Piroxicam (284)</td><td>RR = 1.66 [1.14; 2.44]</td></tr><tr><td>Tenoxicam (n=310)</td><td>RR = 1.43 [0.40; 5.14]</td></tr><tr><td>Meloxicam (n=1495)</td><td>RR = 1.24 [0.98; 1.56]</td></tr><tr><td>Ibuprofen (n=1384)</td><td>RR = 1.19 [0.93; 1.54]</td></tr><tr><td>NSAID (n=6754)</td><td>RR = 1.55 [1.40; 1.72]</td></tr></table> <table><tr><th colspan="2">RR from combined cohorts</th></tr><tr><td>NSAIDs</td><td>RR = 2.22 [1.70; 2.90]</td></tr><tr><td colspan="2">Related to duration of exposure</td></tr><tr><td>≤ 1 year</td><td>RR = 2.17 [1.76; 2.67]</td></tr><tr><td>2-3 years</td><td>RR = 1.45 [1.19; 1.75]</td></tr></table>	Combined RR from clinical trials (CI95%)		Indomethacin (n=1 357)	RR = 2.25 [1.00; 5.07]	Naproxen (n=792)	RR = 1.83 [1.25; 2.68]	Diclofenac (n=1132)	RR = 1.73 [1.21; 2.46]	Piroxicam (284)	RR = 1.66 [1.14; 2.44]	Tenoxicam (n=310)	RR = 1.43 [0.40; 5.14]	Meloxicam (n=1495)	RR = 1.24 [0.98; 1.56]	Ibuprofen (n=1384)	RR = 1.19 [0.93; 1.54]	NSAID (n=6754)	RR = 1.55 [1.40; 1.72]	RR from combined cohorts		NSAIDs	RR = 2.22 [1.70; 2.90]	Related to duration of exposure		≤ 1 year	RR = 2.17 [1.76; 2.67]	2-3 years	RR = 1.45 [1.19; 1.75]
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2-3 years	RR = 1.45 [1.19; 1.75]																															
Richy (2007)	- Meta-analysis of 75 published clinical trials (1980-2006) - piroxicam was evaluated in 45 trials (17 165 patients) - Aim: to reassess the efficacy/tolerance profile of piroxicam in comparison with 7 other NSAIDs	Major GI events (perforation, ulcer and bleeding)	7 other NSAIDs (not specified in the CHMP report)	Combined OR of risk of major GI events for patients exposed to piroxicam compared with other NSAIDs: OR = 1.33 [0.96; 1.84]																												

Table 1 (continued)

Ref	Type of study	Effect studied	Comparators	Result																											
Singh (2004)	▪ Combined analysis of 28 clinical trials selected on the following criteria: - at least one group treated with meloxicam - treatment duration ≥ 21 days - population ≥ 20 per treatment arm - publication before 1999 - included patients at risk of gastrointestinal bleeding ▪ 24 196 patients (13 118 on meloxicam, 5 371 on piroxicam, 5 464 on diclofenac and 243 on naproxen) ▪ Kaplan-Meier survival analysis of serious undesirable GI events and thromboembolism ▪ Aim: to evaluate the risk of serious undesirable GI effects with piroxicam at the recommended doses.	Serious GI complication: - gastric or duodenal perforation - pyloric or duodenal stenosis - GI bleeding with serious repercussions on haemodynamic status	- Meloxicam* (15 mg/day) - Diclofenac (100-150 mg/day) - Piroxicam (20 mg/day) - Naproxen (1000 mg/day)	Cumulative risk of serious GI complication for duration of exposure < 60 days <table><tr><th>NSAIDs</th><th>Cumulative risk</th><th>Number of events</th></tr><tr><td>Piroxicam</td><td>0.9%</td><td>15</td></tr><tr><td>Naproxen</td><td>0.5%</td><td>1</td></tr><tr><td>Meloxicam 15 mg/day</td><td>0.2%</td><td>5</td></tr><tr><td>Diclofenac</td><td>0.1%</td><td>7</td></tr></table> Paired comparison of drugs for duration < 60 days <table><tr><th>Drugs compared</th><th>p</th></tr><tr><td>meloxicam vs. diclofenac</td><td>0.9</td></tr><tr><td>meloxicam vs. piroxicam</td><td>0.03</td></tr><tr><td>meloxicam vs. naproxen</td><td>0.5</td></tr><tr><td>diclofenac vs. piroxicam</td><td>0.09</td></tr><tr><td>piroxicam vs. naproxen</td><td>0.7</td></tr></table> p: log-rank test Onset of serious GI competition differed significantly between meloxicam and piroxicam. In contrast, there was no significant difference between diclofenac and piroxicam or between piroxicam and naproxen.	NSAIDs	Cumulative risk	Number of events	Piroxicam	0.9%	15	Naproxen	0.5%	1	Meloxicam 15 mg/day	0.2%	5	Diclofenac	0.1%	7	Drugs compared	p	meloxicam vs. diclofenac	0.9	meloxicam vs. piroxicam	0.03	meloxicam vs. naproxen	0.5	diclofenac vs. piroxicam	0.09	piroxicam vs. naproxen	0.7
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Gaffney (1998)	- Meta-analysis of 38 randomised trials (i.e. 15 208 patients) - Aim: to evaluate the efficacy and GI toxicity of Piroxicam 20 mg compared with other NSAIDs in chronic and acute conditions.	2 measures of GI toxicity: - proportion of patients with GI side effects - proportion of patients with GI bleeding or GI ulcer	8 other NSAIDs: naproxen, diclofenac, nabumetone, ibuprofen, tenoxicam, indomethacin, etodolac and oxaprozin	- No increase in global frequency of GI events for piroxicam, in chronic or acute conditions. - Bleeding and ulcers were not sufficiently common to reach significance (15/3020 for piroxicam and 20/7221 for NSAIDs). - Crude RR for piroxicam vs. other NSAIDs was 1.79 with CI95% = [0.92; 3.50], so non-significant. - No GI bleeding or ulcers in acute conditions.																											

* : Two dosages were studied for meloxicam, i.e. 7.5 and 15 mg. The results presented concern only the dose of 15 mg as this is the recommended dose for first line therapy in the treatment of RA and AS.

Table 2: Summary of meta-analyses of observational studies of gastrointestinal side effects of piroxicam

Ref.	Type of study	Effect studied	Comparators	Result	
Hernandez-Diaz (2000)	- Meta-analysis of 18 studies (1990-1998): 15 case-control studies and 3 observational studies - Aim: to evaluate the risk of upper GI complications by type of NSAID or according to individual risk factors	Perforation or upper GI bleeding, or upper GI events leading to admission to hospital or consultation with a specialist	8 NSAIDs: Azapropazone, piroxicam, ketoprofen, indomethacin, naproxen, ibuprofen, sulindac, diclofenac	Risk factors for GI complication: age, GI history, sex, recent introduction of treatment, dose	
				NSAID (number of studies concerned)	Pooled RR for upper GI complications for NSAID users vs. non-users
				Azapropazone (2)	27.5 [12.0; 62.9]
				Piroxicam (12)	6.3 [5.5; 7.2]
				Ketoprofen (6)	4.6 [3.3; 6.4]
				Indomethacin (10)	4.6 [3.8; 5.5]
				Naproxen (12)	4.0 [3.5; 4.6]
				Sulindac (6)	3.6 [2.8; 4.7]
				Diclofenac (11)	3.3 [2.8; 3.9]
				Ibuprofen (9)	1.9 [1.6; 2.2]
				All NSAIDs (18)	3.8 [3.6; 4.1]

Table 3: Summary of observational studies not included in the previous meta-analyses evaluating gastrointestinal side effects

Ref.	Type of study	Effect studied	Results		
Gallerani (2004)	- Cross-sectional study, - 32 388 patients (mean age = 70+/- 15 years) Registry data (GIFA: Italian Group of Pharmacoepidemiology in the Elderly) - Aim: to evaluate the relationships between clinical factors, medicine-taking at home, and risk of admission to hospital for upper GI bleeding	Upper GI bleeding: -Diagnosis of bleeding of the oesophagus, stomach or duodenum, or bleeding peptic ulcer, -Haematemesis, melaena, anaemia or shock with confirmation of acute GI or oesophageal disease	Adjusted OR associated with risk of upper GI pleading		
			Drug	Number of cases (% population)	Adjusted OR
			Piroxicam	22 (2.3%)	4.76 [2.98; 7.60]
			Indomethacin	10 (1.1%)	3.12 [1.63; 5.38]
			Ketorolac	15 (1.6%)	2.45 [1.44; 4.15]
			Naproxen	6 (0.6%)	2.15 [0.92; 4.89]
			Indobufen	19 (2.0%)	1.81 [0.62; 5.25]
			Diclofenac	40 (4.3%)	1.80 [1.29; 2.51]
			Nimesulide	6 (0.6%)	1.41 [0.61; 3.25]
			All NSAIDs	95 (10.1%)	2.06 [1.65; 2.85]
Mellemkjaer (2002)	- Historic cohort study - 156 138 exposed to NSAIDs - Aim: to evaluate the association and increased risk of upper GI bleeding associated with NSAIDs, by comparing frequency of onset in the population studied (O) to that expected in the general population (E), by calculating a ratio O/E.	Upper GI bleeding: oesophagitis, gastritis, gastric, duodenal, gastroduodenal or gastrojejunal ulcer, haematemesis, melaena or unspecified GI bleeding	O/E ratio for risk of upper GI bleeding		
				Number of cases	O/E
			Ketoprofen	42	6.30 [4.5; 8.5]
			Piroxicam	28	5.00 [3.3; 7.2]
			Diclofenac	43	4.87 [3.5; 6.6]
			Indomethacin	33	4.28 [2.9; 6.0]
			Naproxen	35	3.03 [2.1; 4.2]
			Ibuprofen	112	2.41 [2.0; 2.9]

Table 3 (continued):

Ref.	Type of study	Effect studied	Results				
Laporte (2004)	- Case-control study (1998-2001) - 2 813 cases, 7 193 hospital controls - Aim: to evaluate the risk of upper GI bleeding associated with the use of analgesics and NSAIDs, with a special focus on new drugs	Upper GI bleeding: all patients admitted with a diagnosis of acute upper GI bleeding caused by a gastric or duodenal ulcer, acute lesion of the gastric mucosa, erosive duodenitis or mixed lesions.	OR associated with risk of upper GI bleeding				
				cases	controls	OR	
			Ketorolac	33	6	24.7 [8.0; 77.0]	
			Piroxicam	119	40	15.5 [10.0; 24.2]	
			Ketoprofen	16	9	10.0 [3.9; 25.8]	
			Indomethacin	29	16	10.0 [4.4; 22.6]	
			Naproxen	52	27	10.0 [5.7; 17.6]	
			Aspirin	591	403	8.0 [6.7; 9.6]	
			Rofecoxib	10	10	7.2 [2.3; 23.0]	
			Meloxicam	14	11	5.7 [2.2; 15.0]	
			Dexketoprofen	16	8	4.9 [1.7; 13.9]	
			Diclofenac	100	98	3.7 [2.6; 5.4]	
			Nimesulide	48	46	3.2 [1.9; 5.6]	
			Ibuprofen	60	58	3.1 [2.0; 4.9]	
			Aceclofenac	15	30	1.4 [0.6; 3.3]	
Lanas (2003)	- Case-control study (1995-1998) - 1 122 cases, 2 231 controls (general and hospital population) - Primary aim: to evaluate the effect of nitrovasodilators on risk of upper GI bleeding associated with NSAIDs and low-dose aspirin	Upper GI bleeding: All patients admitted to hospital with bleeding from a peptic lesion (including ulcers, erosions and acute mucosal lesions)	OR associated with risk of upper GI bleeding				
				cases	con trols	Crude OR	OR adjusted for risk factors
			Ketorolac	12	1	24.1 [3.1; 185.6]	56.7 [7.2; 444]
			Piroxicam	51	11	9.6 [4.9; 18.5]	18.5 [9.2; 36.9]
			Aspirin	323	248	3.2 [2.7; 3.8]	6.6 [5.2; 8.2]
			Naproxen	21	16	2.6 [1.3; 5.1]	5.3 [2.6; 10.8]
			Diclofenac	40	35	2.3 [1.4; 3.6]	5.1 [3.1; 8.4]
			Paracetamol	39	101	0.75 [0.52; 1.10]	0.6 [0.4; 1.0]

Table 3 (continued):

Ref	Type of study:	Effect studied	Results																																																				
Lanas (2006)	- Case-control study (2001-2004) - 2 777 cases, 5 532 hospital controls - Aim: to quantify the risk of upper GI bleeding associated with coxib therapy in everyday practice. Secondary aims: to quantify and compare the risks of upper GI bleeding with traditional NSAIDs, aspirin, platelet antiaggregants and anticoagulants.	upper GI bleeding: patient admitted to hospital following GI bleeding (haematemesis or melaena), confirmed by endoscopy showing a peptic ulcer lesion.	<table><tr><th colspan="4">OR associated with risk of upper GI bleeding</th></tr><tr><th></th><th>cases</th><th>controls</th><th>OR adjusted for risk factors</th></tr><tr><td>Non-users of NSAIDs</td><td>2017</td><td>4693</td><td>Reference</td></tr><tr><td>Ketorolac</td><td>24</td><td>7</td><td>14.4 [5.2; 39.9]</td></tr><tr><td>Piroxicam</td><td>98</td><td>32</td><td>12.6 [7.8; 20.3]</td></tr><tr><td>Meloxicam</td><td>20</td><td>13</td><td>9.8 [4.0; 23.8]</td></tr><tr><td>Indomethacin</td><td>20</td><td>14</td><td>9.0 [3.9; 20.7]</td></tr><tr><td>Ketoprofen</td><td>14</td><td>5</td><td>8.6 [2.5; 29.2]</td></tr><tr><td>Lornoxicam</td><td>9</td><td>6</td><td>7.7 [2.4; 24.4]</td></tr><tr><td>Naproxen</td><td>80</td><td>46</td><td>7.3 [4.7; 11.4]</td></tr><tr><td>Ibuprofen</td><td>174</td><td>162</td><td>4.1 [3.1; 5.3]</td></tr><tr><td>Diclofenac</td><td>126</td><td>140</td><td>3.1 [2.3; 4.2]</td></tr><tr><td>Aceclofenac</td><td>31</td><td>52</td><td>2.6 [1.5; 4.6]</td></tr></table>	OR associated with risk of upper GI bleeding					cases	controls	OR adjusted for risk factors	Non-users of NSAIDs	2017	4693	Reference	Ketorolac	24	7	14.4 [5.2; 39.9]	Piroxicam	98	32	12.6 [7.8; 20.3]	Meloxicam	20	13	9.8 [4.0; 23.8]	Indomethacin	20	14	9.0 [3.9; 20.7]	Ketoprofen	14	5	8.6 [2.5; 29.2]	Lornoxicam	9	6	7.7 [2.4; 24.4]	Naproxen	80	46	7.3 [4.7; 11.4]	Ibuprofen	174	162	4.1 [3.1; 5.3]	Diclofenac	126	140	3.1 [2.3; 4.2]	Aceclofenac	31	52	2.6 [1.5; 4.6]
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