HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

1 April 2009

BREXIN 20 mg, scored tablet
Box of 14 (CIP: 335 959-8)

BREXIN 20 mg, effervescent tablet
Box of 14 (CIP: 348 777-0)

PIERRE FABRE MEDICAMENT

Piroxicam
ATC code: M01AC01

List I

Date of Marketing Authorisation:

- BREXIN 20 mg, scored tablet: 7 August 1992
  BREXIN 20 mg, effervescent tablet: 25 November 1998
- Last correction: 21 May 2008 (the headings Therapeutic Indications, Posology and method of administration, Contraindications, Special warnings and precautions for use, Interactions with other medicinal products and other forms of interactions and Undesirable effects).

Reason for request: Re-evaluation of the actual benefit of piroxicam-based medicinal products for systemic use in accordance with Article R. 163-21 of the Social Security Code. This re-evaluation follows the EMEA arbitration procedure relating to piroxicam-based medicinal products.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Piroxicam

1.2. Indications

Old wording:

"They are based on the anti-inflammatory activity of piroxicam, the importance of the intolerance symptoms to which the medicine gives rise and its place in the range of anti-inflammatory products currently available.

They are limited, in adults and children from 15 years of age, to:

- long-term symptomatic treatment of:
  - chronic inflammatory rheumatism, particularly rheumatoid arthritis, ankylosing spondylitis (or related syndromes, such as Fiessinger-Leroy-Reiter syndrome and psoriatic arthritis),
  - certain painful and disabling forms of osteoarthritis.

- short-term symptomatic treatment of acute episodes of:
  - abarticular rheumatic conditions such as scapulohumeral periarthritis, tendinitis, bursitis,
  - acute posttraumatic conditions affecting the locomotor apparatus,
  - microcrystalline arthritis,
  - osteoarthritis,
  - radiculalgia."

New wording:

"Piroxicam is indicated for the symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis. Because of its safety profile (see section 4.2, 4.3 and 4.4 of the SPC), piroxicam must not be used as first-line treatment when NSAID treatment is indicated.

The decision to prescribe a medicine containing piroxicam must be based on an evaluation of all the specific risks to each patient (see sections 4.3 and 4.4 of the SPC)."

1.3. Dosage

The prescription of medicines containing piroxicam must be initiated by doctors experienced in the diagnosis and treatment of patients with inflammatory or degenerative rheumatic diseases.

This medicine is for use only in adults and children over 15 years of age.

The recommended maximum daily dose is 20 mg.

The occurrence of adverse effects can be minimised by using the lowest possible dose needed to relieve the symptoms in the shortest period of treatment. The benefit and safety of using the treatment must be re-evaluated in 14 days.

If it proves necessary to continue the treatment, it must be subject to frequent re-evaluation.

Since piroxicam has been associated with an increased risk of gastrointestinal complications, the option of using a treatment to protect the gastric mucosa (such as misoprostol or proton pump inhibitors) must be seriously considered, particularly in 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. Medicines in the same therapeutic category

2.2.1. Medicines that are strictly comparable

These are other piroxicam-based medicinal products for systemic use, and their generic forms, the indications for which are restricted to the symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis as second-line treatment when an NSAID treatment has to be prescribed:

- CYCLADOL 20 mg, scored tablet and effervescent tablet
- FELDENE 10 mg, capsule
- - FELDENE 20 mg, capsule, dispersible tablet and suppository
- - FELDENE 20 mg/1 ml, solution for injection
- PROXALYOC 10 and 20 mg, oral lyophilisate

2.2.2. Medicines that are not strictly comparable

These are other medicinal products, and their generic forms, from the oxicam class for systemic use:

- meloxicam : MOBIC 7.5 and 15 mg tablet, 7.5 and 15 mg capsule, 7.5 mg/ml oral suspension, 7.5 and 15 mg suppository and 15 mg/1.5 ml solution for injection
- tenoxicam: TILCOTIL 20 mg tablet, effervescent tablet, suppository and lyophilisate and solution for parenteral use

2.3. Medicines with a similar therapeutic aim:

These are other NSAID medicinal products (indoles and derivatives, arylcarboxyls, fenamates, pyrazoles, selective COX-2 inhibitors and others) and steroidal anti-inflammatories.

3 ANALYSIS OF AVAILABLE DATA

Reminder of the background:
Following an application from the European Commission, the Committee for Medicinal Products for Human Use (CHMP) re-examined the safety 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 that 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-derivative 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 safety 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 doctor with experience in the management of patients with degenerative or inflammatory rheumatic disorders. In all cases, the treatment must be reassessed at the end of 14 days' treatment.
- Doctors 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 adverse effects of piroxicam 20 mg by 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, non significant difference).

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

3.2. Adverse effects

3.2.1. Gastrointestinal adverse effects

- **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 versus 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 studies[4], the main inclusion criterion for which was that they had to have 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 studies[5] (15,208 patients analysed for safety), 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 (15/3020 with piroxicam and 20/7221 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 details are available of this study, which was presented at a conference.

Richy (2007)[6] :
This meta-analysis included 75 clinical studies[5], 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 conference.

- **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).

[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.ecceo7.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

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 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], Lanas (2003)[11] and Lanas (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 safety of piroxicam is based on 2 case-control studies: Roujeau (1993)[13] and Mokenhaupt (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: crude RR = 34; 95% CI = [11; 105]
- tenoxicam: crude RR = 43; 95% CI = [12; 145]
- piroxicam: crude 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]

[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] Lanas 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] Lanas 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

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

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

- oxicams ≤ 2 months: crude RR = 72; 95% CI = [25; 209]
- oxicams > 2 months: crude RR = 0; 95% CI = [0; 47]
- propionic acid derivatives ≤ 2 months: gross RR = 5.4; 95% CI = [2.4; 12]
- propionic acid derivatives > 2 months: gross 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 safety 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 for 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 relating to 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.

[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

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 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 the most serious 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 safety 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 medicines 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 large.

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 BREXIN will have a positive impact on morbidity and mortality.

Consequently, it is not expected that BREXIN 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 BREXIN 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%

APPENDICES

Table 1: Summary of meta-analyses of clinical studies which examined the gastrointestinal safety of piroxicam

<table>
<tr><th>Ref.</th><th>Type of study</th><th>Effect studied</th><th>Comparators</th><th>Results</th></tr>
<tr>
<td>Richy (2004)</td>
<td>- Meta-analysis of 32 randomised controlled clinical studies and 13 controlled observational studies (1985-2003)

- 3 randomised controlled clinical studies versus placebo or non-users of NSAIDs (284 patients) which evaluated piroxicam

- Aim: to evaluate the risk of GI complications of the main NSAIDs, particularly as a function of the period of exposure.</td>
<td>➔<u>Depending on the studies, 2 types of endpoints</u>:
- minor GI event (abdominal pain, nausea, constipation, diarrhoea and dyspepsia).
- major GI event (gastric, duodenal or intestinal ulcer, haemorrhage, perforation, drug-related hospitalisation and death).

➔<u>Endpoints of the 3 piroxicam studies</u>: minor GI complication (29 patients), or major (229 patients), or severe GI complications (26 patients)</td>
<td>indomethacin,
naproxen,
diclofenac,
piroxicam,
tenoxicam,
meloxicam
ibuprofen

Comparison with a placebo control: placebo or group not exposed to NSAIDs</td>
<td>Risk of GI complication in patients on NSAIDs compared to patients not exposed to NSAIDs or on placebo
<table>
<tr><th colspan="2">Combined RR from clinical studies (95% CI)</th></tr>
<tr><td>Indomethacin (n = 1357)</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">Population-based combined RRs</th></tr>
<tr><td>NSAID</td><td>RR = 2.22 [1.70; 2.90]</td></tr>
<tr><td colspan="2">As a function of period of exposure:</td></tr>
<tr><td>≤ 1 year</td><td>RR = 2.17 [1.76; 2.67]</td></tr>
<tr><td>Between 2 and 3 years</td><td>RR = 1.45 [1.19; 1.75]</td></tr>
</table>
</td>
</tr>
<tr>
<td>Richy (2007)</td>
<td>- Meta-analysis of 75 published clinical studies (1980-2006)
- 45 studies (17,165 patients) which evaluated piroxicam
- Aim: to re-evaluate the efficacy/safety profile of piroxicam by comparison with 7 other NSAIDs</td>
<td>Major GI events (perforation, ulcer and haemorrhage)</td>
<td>7 other NSAIDs (not specified in the CHMP report)</td>
<td>Combined OR for the risk of major GI events for patients exposed to piroxicam compared to other NSAIDs:

OR = 1.33 [0.96; 1.84]</td>
</tr>
</table>

Table 1 (continued)

<table>
<tr><th>Ref.</th><th>Type of study</th><th>Effect studied</th><th>Comparators</th><th>Result</th></tr>
<tr>
<td>Singh (2004)</td>
<td>▪ Combined analysis of 28 clinical studies selected according to the following criteria:
- at least one meloxicam treatment group
- duration of treatment ≥ 21 D
- population ≥ 20 per treatment arm
- publication earlier than 1999
- patients included at risk of gastro-intestinal haemorrhage

▪ 24,196 patients (13,118 under meloxicam, 5371 under piroxicam, 5464 under diclofenac and 243 under naproxen)

▪ Kaplan-Meier survival analysis of the onset of serious GI adverse events and thromboembolic complications

▪ Aim: to evaluate the risk of serious GI adverse effects with piroxicam in the recommended doses.</td>
<td>Serious GI complication:
- gastric or duodenal perforation
- pyloroduodenal stenosis
- GI haemorrhage with major haemodynamic impact.</td>
<td>- Meloxicam* (15 mg/d)
- Diclofenac (100-150 mg/d)
- Piroxicam (20 mg/d)
- Naproxen (1000 mg/d)</td>
<td>Cumulative risk of serious GI complication for a period of exposure of < 60 days
<table>
<tr><th>NSAID</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/d</td><td>0.2%</td><td>5</td></tr>
<tr><td>Diclofenac</td><td>0.1%</td><td>7</td></tr>
</table>
Two-by-two comparison of treatments for a duration of < 60 days
<table>
<tr><th>Substances 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
Changes in the occurrence of serious GI complications are significantly different between meloxicam and piroxicam.
On the other hand, there is no significant difference between diclofenac vs piroxicam and piroxicam vs naproxen.</td>
</tr>
<tr>
<td>Gaffney (1998)</td>
<td>- Meta-analysis of 38 randomized studies (15,208 patients)
- Aim: to evaluate the efficacy and GI toxicity of piroxicam 20 mg as compared to other NSAIDs in chronic and acute conditions.</td>
<td>2 measures of GI toxicity:
- proportion of patients with GI side effects
- proportion of patients with a GI haemorrhage or GI ulcer</td>
<td>8 other NSAIDs: naproxen, diclofenac, nabumetone, ibuprofen, tenoxicam, indomethacin, etodolac and oxaprozin</td>
<td>- No increase in the overall frequency of GI events for piroxicam in chronic or acute settings.
- Haemorrhages and ulcers were not sufficiently frequent to reach the significance level (15/3020 for piroxicam and 20/7221 for other NSAIDs).
- The crude RR for piroxicam vs other NSAIDs was 1.79 with a 95% CI = [0.92; 3.50], it is therefore not significant.
- No GI haemorrhage or ulcer in acute conditions.</td>
</tr>
</table>

*: Two dosages were studied for meloxicam: 7.5 and 15 mg. The results presented concern only the 15 mg dosage since it corresponds to the recommended dose for first-line treatment of RA and AS.

Table 2: Summary of meta-analyses of observational studies which evaluated the gastrointestinal safety of piroxicam

<table>
<tr><th>Ref.</th><th>Type of study</th><th>Effect studied</th><th>Comparators</th><th>Result</th></tr>
<tr><td>Hernandez-Diaz (2000)</td><td>- Meta-analysis of 18 studies (1990-1998): 15 case-control studies and 3 observation studies

- Aim: to evaluate the risk of upper GI complication according to type of NSAID or according to individual risk factors</td><td>Upper GI perforation or haemorrhage, or upper GI event leading to hospitalisation or consultation of a specialist</td><td>8 NSAIDs
Azapropazone, piroxicam, ketoprofen, indomethacin, naproxen, ibuprofen, sulindac, diclofenac</td><td>Risk factors for GI complications: age, GI medical history, sex, recent introduction of treatment, dose
<table>
<tr><th>NSAID (number of studies concerned)</th><th>Pooled RR of upper GI complications for users of NSAIDs vs non-users</th></tr>
<tr><td>Azapropazone (2)</td><td>27.5 [12.0; 62.9]</td></tr>
<tr><td>Piroxicam (12)</td><td>6.3 [5.5; 7.2]</td></tr>
<tr><td>Ketoprofen (6)</td><td>4.6 [3.3; 6.4]</td></tr>
<tr><td>Indomethacin (10)</td><td>4.6 [3.8; 5.5]</td></tr>
<tr><td>Naproxen (12)</td><td>4.0 [3.5; 4.6]</td></tr>
<tr><td>Sulindac (6)</td><td>3.6 [2.8; 4.7]</td></tr>
<tr><td>Diclofenac (11)</td><td>3.3 [2.8; 3.9]</td></tr>
<tr><td>Ibuprofen (9)</td><td>1.9 [1.6; 2.2]</td></tr>
<tr><td>All NSAIDs (18)</td><td>3.8 [3.6; 4.1]</td></tr>
</table></td></tr>
</table>

Table 3: Summary of observational studies not included in the earlier meta-analyses which evaluated gastrointestinal safety

<table>
<tr><th>Ref</th><th>Type of study</th><th>Effect studied</th><th>Results</th></tr>
<tr><td>Gallerani (2004)</td><td>- Cross-sectional study

- 32,388 patients (mean age: 70 ± 15 years)
Data from a registry (GIFA: Italian pharmacovigilance group in elderly subjects)

- Aim: to evaluate the relationships between clinical parameters, taking the medication at home, and the risk of hospitalisation with upper GI haemorrhage</td><td>Upper GI haemorrhage:

-diagnosis of oesophageal, gastric or duodenal haemorrhage, or haemorrhagic peptic ulcer,

-Haematemesis, melaena, anaemia or shock with confirmation of an acute oesophago-GI disease</td><td>
<table>
<tr><th colspan="3">Adjusted OR associated with risk of upper GI haemorrhage</th></tr>
<tr><td>Substance</td><td>Number of cases (% of population)</td><td>Adjusted OR</td></tr>
<tr><td>Piroxicam</td><td>22 (2.3%)</td><td>4.76 [2.98; 7.60]</td></tr>
<tr><td>Indomethacin</td><td>10 (1.1%)</td><td>3.12 [1.63; 5.38]</td></tr>
<tr><td>Ketorolac</td><td>15 (1.6%)</td><td>2.45 [1.44; 4.15]</td></tr>
<tr><td>Naproxen</td><td>6 (0.6%)</td><td>2.15 [0.92; 4.89]</td></tr>
<tr><td>Indobufen</td><td>19 (2.0%)</td><td>1.81 [0.62; 5.25]</td></tr>
<tr><td>Diclofenac</td><td>40 (4.3%)</td><td>1.80 [1.29; 2.51]</td></tr>
<tr><td>Nimesulide</td><td>6 (0.6%)</td><td>1.41 [0.61; 3.25]</td></tr>
<tr><td>All NSAIDs</td><td>95 (10.1%)</td><td>2.06 [1.65; 2.85]</td></tr>
</table>
</td></tr>
<tr><td>Mellemkjaer (2002)</td><td>- Historical cohort study

- 156,138 persons exposed to NSAIDs

- Aim: to evaluate the connection and excess risk of upper GI haemorrhage associated with NSAIDs by comparing the frequency of occurrence of haemorrhage in the population studied (O) with that expected in the general population (E) by calculating an O/E ratio.</td><td>Upper GI haemorrhage:
œsophagitis, gastritis, gastric, duodenal, gastroduodenal or gastrojejunal ulcer,
haematemesis, melaena, or unspecified GI haemorrhage</td><td>
<table>
<tr><th colspan="3">O/E ratio of the risk of upper GI haemorrhage</th></tr>
<tr><td></td><td>Number of cases observed</td><td>O/E</td></tr>
<tr><td>Ketoprofen</td><td>42</td><td>6.30 [4.5; 8.5]</td></tr>
<tr><td>Piroxicam</td><td>28</td><td>5.00 [3.3; 7.2]</td></tr>
<tr><td>Diclofenac</td><td>43</td><td>4.87 [3.5; 6.6]</td></tr>
<tr><td>Indomethacin</td><td>33</td><td>4.28 [2.9; 6.0]</td></tr>
<tr><td>Naproxen</td><td>35</td><td>3.03 [2.1; 4.2]</td></tr>
<tr><td>Ibuprofen</td><td>112</td><td>2.41 [2.0; 2.9]</td></tr>
</table>
</td></tr>
</table>

Table 3 (continued)

<table>
<tr><th>Ref</th><th>Type of study</th><th>Effect studied</th><th>Results</th></tr>
<tr><td>Laporte, (2004)</td><td>- Case-control study (1998-2001)

- 2813 cases, 7193 hospital controls

- Aim: to evaluate the risk of upper GI haemorrhage associated with use of analgesics and NSAIDs, with special reference to new substances</td><td>Upper GI haemorrhage:
all cases admitted with a diagnosis of acute upper GI haemorrhage from a gastric or duodenal ulcer, an acute lesion of the gastric mucosa, erosive duodenitis or mixed lesions.</td><td>
<table>
<tr><th colspan="4">OR associated with the risk of upper GI haemorrhage</th></tr>
<tr><th></th><th>Cases</th><th>Controls</th><th>OR</th></tr>
<tr><td>Ketorolac</td><td>33</td><td>6</td><td>24.7 [8.0; 77.0]</td></tr>
<tr><td>Piroxicam</td><td>119</td><td>40</td><td>15.5 [10.0; 24.2]</td></tr>
<tr><td>Ketoprofen</td><td>16</td><td>9</td><td>10.0 [3.9; 25.8]</td></tr>
<tr><td>Indomethacin</td><td>29</td><td>16</td><td>10.0 [4.4; 22.6]</td></tr>
<tr><td>Naproxen</td><td>52</td><td>27</td><td>10.0 [5.7; 17.6]</td></tr>
<tr><td>Aspirin</td><td>591</td><td>403</td><td>8.0 [6.7; 9.6]</td></tr>
<tr><td>Rofecoxib</td><td>10</td><td>10</td><td>7.2 [2.3; 23.0]</td></tr>
<tr><td>Meloxicam</td><td>14</td><td>11</td><td>5.7 [2.2; 15.0]</td></tr>
<tr><td>Dexketoprofen</td><td>16</td><td>8</td><td>4.9 [1.7; 13.9]</td></tr>
<tr><td>Diclofenac</td><td>100</td><td>98</td><td>3.7 [2.6; 5.4]</td></tr>
<tr><td>Nimesulide</td><td>48</td><td>46</td><td>3.2 [1.9; 5.6]</td></tr>
<tr><td>Ibuprofen</td><td>60</td><td>58</td><td>3.1 [2.0; 4.9]</td></tr>
<tr><td>Aceclofenac</td><td>15</td><td>30</td><td>1.4 [0.6; 3.3]</td></tr>
</table>
</td></tr>
<tr><td>Lanas (2003)</td><td>- Case-control study (1995-1998)

- 1122 cases, 2231 controls (general population and hospital)

- Main aim: to evaluate the effect of nitrate vasodilators on the risk of upper GI haemorrhage associated with NSAIDs and low-dose aspirin</td><td>Upper GI haemorrhage:
all patients admitted to hospital with haemorrhage from a peptic lesion (including ulcers, erosions and acute mucosal lesions)</td><td>
<table>
<tr><th colspan="5">OR associated with the risk of upper GI haemorrhage</th></tr>
<tr><th></th><th>Cases</th><th>Controls</th><th>Crude OR</th><th>OR adjusted for risk factors</th></tr>
<tr><td>Ketorolac</td><td>12</td><td>1</td><td>24.1 [3.1; 185.6]</td><td>56.7 [7.2; 444]</td></tr>
<tr><td>Piroxicam</td><td>51</td><td>11</td><td>9.6 [4.9; 18.5]</td><td>18.5 [9.2; 36.9]</td></tr>
<tr><td>Aspirin</td><td>323</td><td>248</td><td>3.2 [2.7; 3.8]</td><td>6.6 [5.2; 8.2]</td></tr>
<tr><td>Naproxen</td><td>21</td><td>16</td><td>2.6 [1.3; 5.1]</td><td>5.3 [2.6; 10.8]</td></tr>
<tr><td>Diclofenac</td><td>40</td><td>35</td><td>2.3 [1.4; 3.6]</td><td>5.1 [3.1; 8.4]</td></tr>
<tr><td>Paracetamol</td><td>39</td><td>101</td><td>0.75 [0.52; 1.10]</td><td>0.6 [0.4; 1.0]</td></tr>
</table>
</td></tr>
</table>

Table 3 (continued)

<table>
<tr><th>Ref</th><th>Type of study</th><th>Effect studied</th><th>Results</th></tr>
<tr>
<td>Lanas (2006)</td>
<td>- Case-control study (2001-2004)

- 2777 cases, 5532 hospital controls

- Aim: to quantify the risk of upper GI haemorrhage associated with coxib treatment used in everyday practice.
Secondary aims: to quantify and compare the risks of upper GI haemorrhage with traditional NSAIDs, aspirin, platelet aggregation inhibitors and anticoagulants.</td>
<td>Upper GI haemorrhage:
patient hospitalised following a GI bleed (haematemesis or melaena), confirmed by endoscopy showing an ulcerous peptic lesion.</td>
<td>
<table>
<tr><th colspan="4">OR associated with the risk of upper GI haemorrhage</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>
</td>
</tr>
</table>