HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 October 2009

CELEBREX 100 mg capsule
B/30 (CIP: 354 368.1)

CELEBREX 200 mg capsule
B/30(CIP: 354 370.6)

Applicant: PFIZER

Celecoxib

ATC Code: M01AH01

List I

Date of marketing authorisation: 24 May 2000 (mutual recognition)

Most recent amendments to marketing authorisation:

09/07/2007: Extension of indication in ankylosing spondylitis.
10/06/2009: Amendment to sections of the SPC (dosage, special warnings and precautions for use, interactions, pregnancy and lactation, undesirable effects, pharmacodynamic properties, pharmacokinetic properties)

Reason for request: Inclusion on the list of products reimbursed by National Insurance and for hospital use in the extension of indication: "Symptomatic relief in the treatment of ankylosing spondylitis".

Medical, Economic and Public Health Assessment Division

CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

Celecoxib

1.2. Indications

"Symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis **and ankylosing spondylitis**. The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks. "

1.3. Dosage

"As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

Osteoarthritis

The usual recommended daily dose is 200 mg taken once daily or in two divided doses. In some patients, with insufficient relief from symptoms, an increased dose of 200 mg twice daily may increase efficacy.
In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

Rheumatoid arthritis

The initial recommended daily dose is 200 mg taken in two divided doses.

The dose may, if needed, later be increased to 200 mg twice daily. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

Ankylosing spondylitis

The recommended daily dose is 200 mg taken once daily or in two divided doses. In a few patients, with insufficient relief from symptoms, an increased dose of 400mg once daily or in two divided doses may increase efficacy. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

The maximum recommended daily dose is 400 mg for all indications.
Celebrex may be taken with or without food.

- Elderly: (>65 years)

As in younger adults, 200 mg per day should be used initially. The dose may, if needed, later be increased to 200 mg twice daily. Particular caution should be exercised in elderly with a body weight less than 50 kg.

- Hepatic impairment

Treatment should be initiated at half the recommended dose in patients with established moderate liver impairment with a serum albumin of 25-35 g/L. Experience in such patients is limited to cirrhotic patients.

- Renal impairment

Experience with celecoxib in patients with mild or moderate renal impairment is limited; therefore such patients should be treated with caution.

- Children

Celecoxib is not indicated for use in children.

CYP2C9 Poor Metabolisers

Patients who are known, or suspected to be CYP2C9 poor metabolisers based on genotyping or previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as the risk of dose-dependent adverse effects is increased. Consider reducing the dose to half the lowest recommended dose. "

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

M:	Musculo-skeletal system
M01:	Anti-inflammatory and antirheumatic products
M01A:	Anti-inflammatory and antirheumatic products, non-steroids
M01AH:	Coxibs
M01AH01:	Celecoxib

2.2. Medicines in the same therapeutic category

Comparator medicines

Other NSAIDs indicated in the symptomatic treatment of ankylosing spondylitis.

2.3. Medicines with a similar therapeutic aim

These are:

- other immediate-action symptomatic treatments, in other words all non-anti-inflammatory analgesics indicated in the management of non-cancer chronic pain;
- disease-modifying treatments, in particular TNFα inhibitors etanercept (Enbrel), adalimumab (Humira) and infliximab (Remicade).

3 ANALYSIS OF AVAILABLE DATA

4.1 Efficacy

The efficacy of celecoxib at a dosage of 200 mg or 400 mg daily in the treatment of ankylosing spondylitis (AS) was evaluated in 1645 patients who were included in four clinical studies, lasting between 6 and 12 weeks.

4.1.1 Superiority studies versus placebo and active comparator (Dougados et al 2001[1] and Barkhuizen et al 2006[2])

Two randomised double-blind studies controlled versus placebo and an active comparator, with the main aim of evaluating the efficacy of celecoxib in the treatment of AS.
One of the secondary objectives was to compare celecoxib with another NSAID (ketoprofen in the study by Dougados, and naproxen in the Barkhuizen study). All patients were able to receive paracetamol 500 mg as an emergency treatment if they had pain (2-6 doses per day).

The main inclusion criteria were:
- Active AS according to the modified New York criteria,
    - o with axial disease
    - o with or without enthesitis
    - o with no peripheral joint involvement (except for hip and/or shoulder),
    - o with a VAS score ≥ 40 mm (Dougados study) or ≥ 50 mm (Barkhuizen study) and an increase in pain of at least 30% after cessation of NSAID treatment.

The primary endpoint when judging efficacy was progression between inclusion and end of treatment (6 weeks in the Dougados study and 12 weeks in the Barkhuizen study) in:
- pain intensity, measured on a visual analogue scale (VAS) of 0-100 mm;
- evaluation by the patient of disease activity[3] on a VAS (in the Barkhuizen study only);
- functional impairment measured using the BASFI index[4].

Results:

Dougados study:
The two hundred and forty-six (246) patients included in this study had a mean age of 39 years, with the majority being men (69%), and had been diagnosed with AS a mean of 11 years previously.

1Dougados M *et al*. Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal anti-inflammatory drug. Arthritis & Rheumatism, 2001; (1) : 180-185.
2Barkhuizen A *et al*. Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis. The Journal of Rheumatology 2006 ; 33 (9) : 1805-1812.
3 evaluation by the patient of disease activity on a 100 mm VAS, in response to the following question: "What is your evaluation of the activity of your disease over the last 2 days, considering your pain and also your difficulties carrying out daily tasks and the effects of your disease on your sexual, social, work and family life? " (0 mm corresponds to no disease activity and 100 mm to extremely active disease).
4 Bath Ankylosing Spondylitis Functional Index, a functional index that uses answers to 10 questions on degree of functional mobility. For each question, the patient evaluates his/her functional mobility on a 0-100 mm VAS, with BASFI index being the mean of the 10 scores.

Table 1. Primary endpoint results of the Dougados study (between day 0 and day 42) - ITT analysis

Numbers	**Placebo** N = 76	**Celecoxib 100 mg twice/day** N = 80	**Ketoprofen 100 mg twice/day** n = 90	Difference p
Pain (VAS 0-100 mm)				
on inclusion	70 ± 15	70 ± 16	66 ± 15	Celecoxib vs placebo, p = 0.007 Ketoprofen vs placebo (p = 0.051) Celecoxib vs ketoprofen, NS
Change at day 42	-12.8 ± 28.8	-27.4 ± 30.1	-21.1 ± 26.1	
BASFI				
on inclusion	42.1 ± 24.6	47 ± 22.9	39.1 ± 18.7	Celecoxib vs plabeco, p = 0.0006 Ketoprofen vs plabeco, p = 0.04 Celecoxib vs ketoprofen, NS
Change at day 42	1.3 ± 17.7	-11.9 ± 22	-6 ± 20.8	

Barkhuizen study

Six hundred and eleven (611) patients were included. They had a mean age of 45 years and a majority were men (74%). Time since diagnosis of AS was not documented.

Table 2. Primary endpoint results of the Barkhuizen study (between day 0 and day 42) - ITT analysis

Numbers	**Placebo** N = 156	**Celecoxib 200 mg once/day** N = 137	**Celecoxib 400 mg once/day** N = 161	**Naproxen 500 mg twice/day** N = 157	Difference p
Pain (VAS 0-100 mm)					Celecoxib 200 vs placebo, celecoxib 400 vs placebo and Napro vs placebo: p < 0.001
on inclusion	73.5 ± 16.6	70.8 ± 15.6	71.4 ± 15.4	71.7 ± 15.6	
Change at day 84	-11.6 ± 27.6	-30.3 ± 27.6	-30.9 ± 28.3	-36.4 ± 30	Naproxen vs celecoxib 200 and Naproxen vs celecoxib 400, NS
Activity					Celecoxib 200 vs placebo, celecoxib 400 vs placebo, Napro vs placebo: p < 0.001
on inclusion	69.1 ± 21.4	65.9 ± 20.5	65.3 ± 22.5	66.1 ± 20.1	
Change at day 84	-6 ± 29	-21.5 ± 29.7	-22.7 ± 28.6	-27.7 ± 30.5	Naproxen vs celecoxib 200: p = 0.04 Naproxen vs celecoxib 400, NS
BASFI					Celecoxib 200 vs placebo, celecoxib 400 vs placebo: p < 0.001
on inclusion	54.4 ± 22.2	50 ± 25	51.7 ± 24.2	52 ± 21.8	
Change at day 84	1.6 ± 22.2	-8.6 ± 19.3	-12.5 ± 22.8	-16.1 ± 26.2	Naproxen vs celecoxib 200, p = 0.006 Naproxen vs celecoxib 400, NS

In both studies, celecoxib given at a daily dosage of 200 mg or 400 mg was superior to placebo in terms of reduction of pain intensity (absolute difference between 14 and 19 points) and improvement in functional mobility (absolute difference between 7 and 11 points).

As a secondary endpoint, comparison of celecoxib with other NSAIDs showed:

- a lack of statistically significant difference between celecoxib 200 mg/day and ketoprofen 200 mg/day in terms of effect on pain and function in the Dougados study;
- a statistically significant difference, with naproxen 500 mg twice daily being superior to celecoxib 200 mg/day in terms of disease activity and function, but not in terms of pain (Barkhuizen studY) and;
- no statistically significant difference between celecoxib 400 mg/day and naproxen 500 mg twice daily in terms of the 3 primary endpoints of the Barkhuizen study.

4.1.2 Non-inferiority studies versus other NSAIDs (Sieper 2007[5] and Kvien 2005 (unpublished)

Two clinical studies lasting 12 weeks, with similar methodology (controlled, randomised, double-blind) were designed to demonstrate non-inferiority of celecoxib administered at dosages of 200 mg/day and 400 mg/day in comparison with diclofenac 150 mg/day.

The main inclusion criteria were as follows:
Active AS according to the modified New York criteria;

- with no peripheral joint involvement (except for hip and/or shoulder);
- with axial disease and;
- having required daily NSAID treatment during the month preceding the study.
- with a VAS score ≥ 40 mm and an increase in pain of at least 30% after cessation of NSAID treatment.

The primary endpoint in the evaluation of efficacy was pain intensity measured on a 100 mm VAS at week 12. The non-inferiority hypothesis was that celecoxib would be considered to be non-inferior to diclofenac if the upper limit of the confidence interval of the difference was less than 10 mm.

Characteristics of patients included in both studies:

In the study by Sieper 2007, 458 patients were included, the majority of whom were men (69.2%) and who had a mean age of 44.8 years. In the study by Kvien 2005, 330 patients were included, the majority of whom were men (72.4%) and who had a mean age of 43.8 years and in whom AS had been diagnosed on average 10 years previously.

5 Sieper J *et al*. Comparison of 2 different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised double-blind controlled study. Ann Rheum Dis. 2008;67(3):323-329.

Results: Per-protocol analysis

Table 3. Results of Sieper (2007) study

Numbers	Celecoxib 200 once daily 126	Celecoxib 200 twice daily 124	Diclofenac 75 mg twice daily 123	Difference
Pain (mm)				
on inclusion	66.5 ± 14.4	67.3 ± 14.9	65.9 ± 13.9	Cele 200 mg once daily vs Diclo: 3.6 ± 3 [-2.3; 9.4].
Change at week 12	-29.8 ± 26.3	-31.7 ± 24.9	-33 ± 25.4	Cele 200 mg twice daily vs Diclo: 1 ± 3 [-5; 6.9]

Table 4. Results of Kvien (2005) study

N	Celecoxib 200 once daily 107	Celecoxib 200 twice daily 108	Diclofenac 50 mg three times daily 115	Difference
Pain (mm)				
on inclusion	66.3 ± 14.1	63.1 ± 16.2	67.0 ± 15.9	Cele 200 mg once daily vs Diclo: 2.3 [-5; 9.7]
Change at week 12	-26.3 ± 23.2	-29.4 ± 26.4	-28.3 ± 25.4	Cele 200 mg twice daily vs Diclo: -2.5 [-9.8; 4.9]

Non-inferiority of celecoxib 200 mg and 400 mg daily in comparison with diclofenac 150 mg/day was demonstrated at 12 weeks in both studies.
However, it is legitimate to question the relevance of a non-inferiority threshold of 10 mm on a 100 mm VAS.

4.1.3 Other data
The applicant has also presented an open-label efficacy study involving 215 patients. This study will not be described here.

4.2 Adverse effects

Data from clinical studies:
No new adverse effects in addition to those mentioned in the SPC have been reported in these studies. The most frequently reported adverse effects were gastro-intestinal. 16.2% with celecoxib and 24.2% with other NSAIDs (diclofenac, ketoprofen and naproxen). 7.1% of patients in the celecoxib arm stopped treatment because of adverse effects , compared with 7.7 % of patients on other NSAIDs.

Pharmacovigilance data
According to PSUR data for the period 1 July 2007 to 31 March 2009, a total of 4076 adverse events were reported.
The most commonly reported adverse effects were: rash, myocardial infarction, gastrointestinal haemorrhage, hypersensitivity and dyspnoea. Analysis of these cases has shown no new information concerning safety.

4.3 Conclusion

The efficacy and safety of celecoxib in the treatment of ankylosing spondylitis at a dosage of 200 or 400 mg per day have been evaluated in 4 clinical studies lasting between 6 and 12 weeks. The primary efficacy endpoint common to all four studies was change in pain intensity measured on a 100 mm VAS. Results of these studies have shown that celecoxib (200 and 400 mg/day) is superior to placebo (absolute difference of between 14 and 19 points in terms of pain reduction) and that it is non-inferior (delta threshold = 10 mm) to diclofenac 150 mg/day. The relevance of this non-inferiority threshold is questionable.
In addition, no difference has been shown between celecoxib and ketoprofen 200 mg/day and naproxen 1 g/day.
Safety was generally in line to the known profile of this product, with main adverse effects being gastro-intestinal. These new safety data do not alter the previous conclusions of the Transparency Committee; they do not provide formal evidence of better digestive safety in terms of serious complications of celecoxib in comparison with non-selective NSAIDs, particularly for at-risk patients.

Overall, the data presented does not provide evidence that celecoxib is more effective or better tolerated than currently available NSAIDs in the treatment of ankylosing spondylitis.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Ankylosing spondylitis is a chronic disease that can be serious and disabling. It often progresses with inflammatory flare-ups, and the main risks in disease progression are vertebral ankylosis, hip involvement and non-bone involvement (particularly cardiac).
Celecoxib is a symptomatic treatment.
Its efficacy/adverse effects ratio in the treatment of ankylosing spondylitis is high.

Public health benefit
In terms of public health, the burden caused by ankylosing spondylitis, a serious and disabling chronic disease, is moderate.
Improvement in therapeutic management of AS is a public health need that is included in the GTNDO objectives6.
According to the available clinical data, this product is not expected to have an additional impact on morbidity and quality of life for patients in comparison with other NSAIDs indicated in the treatment of AS.
However, Celebrex should be able to contribute as much as other NSAIDs to a response to the identified need.
Consequently, CELEBREX is not expected to benefit public health in this indication.

Celebrex, like all NSAIDs, is a first-line treatment.
There are many alternative treatments: all NSAIDs.
The actual benefit of these medicinal products is substantial.

5.2. Improvement in actual benefit

In the treatment of ankylosing spondylitis, CELEBREX does not provide an improvement in actual benefit (IAB V) in comparison with other NSAIDs.

5.3. Therapeutic use

The aim of drug treatment for ankylosing spondylitis is to reduce pain and spinal stiffness in order to preserve or improve functional capacity and quality of life. This primarily involves the use of NSAIDs as first-line symptomatic treatment during flare-ups. If NSAIDs fail or have insufficient effect at the maximal tolerated dose, the patient can be switched to a different NSAID. Analgesics can be given with NSAIDs during flare-ups.
Sulfasalazine and methotrexate only seem to be effective in forms of disease involving the peripheral joints. The efficacy of these products in purely axial forms of disease has not been demonstrated
TNFα inhibitors can be used if NSAIDs fail, have insufficient effect, are poorly tolerated or are contraindicated.

Therapeutic use of CELEBREX:
Celecoxib, like all NSAIDs is a symptomatic first-line treatment for ankylosing spondylitis, with due attention to the contraindications (including pregnancy and women of child-bearing age using no reliable contraception, some heart diseases, progressive peptic ulcer or gastrointestinal bleeding, a history of asthma: see SPC).

6 GTNDO: French National Technical Objective Definition Group (DGS) 2003.

As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. given the available data, the Transparency Committee recommends that treatment routinely be started at a dosage of 200 mg per day. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

5.4. Target Population

According to international data, the prevalence of ankylosing spondylitis is around 0.1%-1.1%. However, according to the epidemiological study carried out by the French Rheumatology Society (2001), the prevalence of ankylosing spondylitis in France, in the population aged 18 and over, seems to be at most around 0.14%[7] or around 65,000 patients.
On this basis, the target population for Celebrex in the ankylosing spondylitis indication would be a maximum of around 65,000 patients.

5.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and/or on the list of medicinal products approved for use by hospitals and various public services in the new indication and at the dosage given in the marketing authorisation.

5.5.1. Packaging: these are appropriate for the prescription conditions

5.5.2. Reimbursement rate: 65 %

7 Saraux A *et al*. Prevalence of spondylarthropathies in 2001. Ann Rheum Dis 2005; 64: 1431-1435.