HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 January 2012

CELEBREX 100 mg, hard capsule
B/30 (CIP code: 354 368-1)

CELEBREX 200 mg, hard capsule
B/30 (CIP code: 354 370-6)

Applicant: PFIZER

celecoxib
ATC code: M01AH01

List I

Date of Marketing Authorisation: 24 May 2000 (mutual recognition)

Date of last amendment: 04 January 2010 (update of the special warnings and undesirable effects concerning in particular serious hepatic reactions reported with celecoxib)

Reason for request: Re-assessment of the actual benefit at the request of the Transparency Committee pursuant to article R 163-21 of the Social Security Code.

Medical, Economic and Public Health Evaluation Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

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 efficacy.
In the absence of an increase in therapeutic benefit after 2 weeks, other therapeutic options should be considered.

Rheumatoid arthritis
The initial recommended daily dose is 200 mg taken in 2 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 2 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 400 mg once daily or in two divided doses may increase efficacy. In the absence of an increase in therapeutic benefit after 2 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.

1.4. Special populations

"Elderly (> 65 years)

As in younger adults, the treatment 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, the treatment should be started at half the recommended dose. Experience such patients is limited to cirrhotic patients.

Renal impairment

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

Children

Celecoxib is not indicated for use in children.

Pregnancy:

No clinical data are available on pregnant women exposed to celecoxib. Studies carried out on animals (rats and rabbits) revealed reproductive toxicity, including malformations.

In humans, the risk during pregnancy is unknown but cannot be ruled out. Like other medicinal products that inhibit prostaglandin synthesis, celecoxib use may lead to uterine inertia and premature closure of the arterial canal in the last trimester of pregnancy. Celecoxib is contraindicated during pregnancy and in women who may become pregnant. If it is discovered that a woman is pregnant during treatment, celecoxib should be stopped.

Breast-feeding:

Patients treated with celecoxib should not breast-feed.

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."

For more information, refer to the SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

M	:	Muscle and skeleton
M01	:	Anti-inflammatory and anti-rheumatic products
M01A	:	Non-steroidal anti-inflammatory and anti-rheumatic products
M01AH	:	Coxibs
M01AH01	:	Celecoxib

2.2. Medicines in the same therapeutic category

These are other non-steroidal, anti-inflammatory products indicated in the symptomatic treatment of osteoarthritis, rheumatoid arthritis (RA) and ankylosing spondylitis (AS).

2.3. Medicines with a similar therapeutic aim

These are other symptomatic treatments with immediate action, i.e. all of the non anti-inflammatory analgesics indicated in chronic non-cancer pain.

3 CONTEXT OF THE ASSESSMENT

Re-assessment of the anti-inflammatories that are selective COX-2 inhibitors (ARCOXIA 30 and 60 mg and CELEBREX) was requested by the Transparency Committee because of concerns about tolerance (cardiovascular, renal, cutaneous and digestive) linked with this class of medicinal product, pursuant to article R 163-21 of the Social Security Code.

As a reminder, on 11 October 2000 the proprietary medicinal products CELEBREX 100 mg and 200 mg obtained an opinion favourable to their inclusion on the list of proprietary medicinal products reimbursable at the pharmacy and at the hospital in the case of osteoarthritis and rheumatoid arthritis. The Transparency Committee had considered that their actual benefit (AB) was substantial and that they provided a moderate improvement in actual benefit (IAB) (level III) in terms of tolerance compared to NSAIDs, except for pyrazoles.

Following the joint submission of the Social Security Division (DSS) and the Ministry of Health DGS in 2002 and the re-assessment of the coxibs by the Committee for Medicinal Products for Human Use (EMEA, February 2004), CELEBREX underwent a second assessment on 16 June 2004. The Committee confirmed that its actual benefit was substantial but downgraded its improvement in actual benefit to minor (level IV) compared to conventional NSAIDs, considering that the better digestive tolerance of CELEBREX compared to anti-cox 1 NSAIDs was minimal.

On 9 May 2007, during the inclusion renewal procedure, the Committee confirmed that the AB was substantial and considered that the data available did not provide formal proof of better digestive tolerance in terms of serious complications of celecoxib compared to non-selective NSAIDs particularly in patients at risk and that there was a cardiovascular risk. Consequently CELEBREX did not provide an IAB (level V) compared to non-selective NSAIDs.
On 21 October 2009, when considering the inclusion of CELEBREX in ankylosing spondylitis (extension of indication), the Committee thought that its AB was substantial, and that it did not provide an IAB compared to other NSAIDs.

During a re-assessment of the IAB at the applicant's request following the submission of new data (CONDOR study), the Committee concluded in its opinion of 15 December 2010 that the new data submitted were unlikely to modify the AB and the level of IAB of CELEBREX attributed on 9 May 2007 in osteoarthritis and rheumatoid arthritis and on 21 October 2009 in ankylosing spondylitis (see table below for details of the opinions).

Table 1. Reminder of previous opinions.

Date of opinion	Request	AB	IAB
11 October 2000	**Inclusion National Insurance and Hospitals in osteoarthritis and RA**	substantial	**IAB III** A trial versus NSAIDs + anti-secretory, or versus NSAIDs + misoprostol would have allowed a better assessment of the advantage in terms of digestive tolerance of this new NSAID. This proprietary medicinal product has a moderate level III IAB in terms of tolerance compared to NSAIDs except for pyrazoles.
16 June 2004	**Re-assessment** following the joint submission of the National Insurance Division and the General Health Division in 2002 and following re-assessment of the coxibs by the Committee for Proprietary Medicinal Products (EMEA, February 2004).	substantial	**IAB IV** An analysis of the results available shows that the better digestive tolerance of CELEBREX compared to anti-cox 1 NSAIDs is minimal, in the current state of the data and the level of proof presented. No notable cardiovascular difference compared to NSAIDs has been noted. Consequently, taking into account better digestive tolerance, this proprietary medicinal product provides a minor IAB (level IV) compared to conventional NSAIDs.
09 May 2007	**Renewal of inclusion** on the list of the proprietary medicinal products refundable by National Insurance	substantial	**IAB V** Taking into account the fact that the data available does not provide formal proof of better digestive tolerance in terms of serious complications of celecoxib compared to non-selective NSAIDs particularly in patients at risk and taking into account that the EMEA recently modified the cardiovascular risk in the SPC, the Transparency Committee considers that this proprietary medicinal product does not provide an IAB (V) compared to non-selective NSAIDs.
21 October 2009	**Inclusion** in the extension of indication of ankylosing spondylitis	substantial	**IAB V** In the treatment of ankylosing spondylitis, CELEBREX does not provide an IAB (V) compared to other NSAIDs.
15 December 2010	**Re-assessment of the IAB** at the request of the applicant	substantial	The Transparency Committee considers that the new data submitted, particularly the results of the CONDOR study, are unlikely to modify the level of improvement in actual benefit of CELEBREX attributed on 09 May 2007 in osteoarthritis and rheumatoid arthritis and on 21 October 2009 in ankylosing spondylitis, i.e.: "CELEBREX does not provide an improvement in actual benefit (V) compared to other NSAIDs."

Within the context of this re-assessment self-referral, which is the subject of this examination, the operating laboratory was asked to provide all of the data available since the previous assessment. The following were provided:

- an update of pharmacovigilance data and;
- data on use.

The literature search department of the HAS carried out an additional bibliographic search on the basis of Medline, Embase and Cochrane data.
The pharmacovigilance department of the Afssaps [French Healthcare Product Safety Agency] was consulted.

4 ANALYSIS OF AVAILABLE DATA

4.1. Efficacy

The applicant provided the results of the study:

Raynauld et al[1] (December 2010)
This longitudinal, open-label study carried out in Canada evaluated the impact of CELEBREX on the loss of cartilaginous volume compared to a modelised historical cohort. CELEBREX was administered to 99 patients suffering from osteoarthritis of the knee at a dose of 200 mg/day for 1 year. The superiority of celecoxib was not demonstrated in this study. The undesirable events reported were considered to be minor.
An analysis of the literature did not identify any new data relating to the efficacy of CELEBREX.

4.2. Adverse effects

4.2.1. Pharmacovigilance data

Between 01 January 2009 and 30 June 2010, 1,432 cases of pharmacovigilance, 972 of which were serious, were reported with celecoxib. The most frequently reported were: skin and subcutaneous tissue disorders, gastrointestinal disorders, general disorders and administration site conditions, and nervous system disorders.

The French SPC is currently being amended to add the undesirable effects: "pulmonary embolism and chest pain" reported during the last PSUR which covered the period from 01 January 2009 to 30 June 2010. This PSUR was already submitted to the Transparency Committee in May 2010. During the period covered by this report, 43 deaths were notified, 7 cases of which were considered to have a possible link with celecoxib, 14 cases of exposure during pregnancy and 7 cases of use in children under 17 years of age.

4.2.2. Data from the literature

The applicant provided a meta-analysis.[2]

This meta-analysis evaluated the cardiovascular tolerance of the NSAIDs. It included 31 trials involving 116,429 patients (MEDAL programme for etoricoxib versus diclofenac). Seven NSAIDs were studied, naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib and lumiracoxib at different doses and in various pathologies.
The primary endpoint was the occurrence of a myocardial infarction.
The secondary endpoints included:

- CV mortality,
- stroke,
- all-cause mortality,
- death of unknown origin.

[1]Raynauld et al. An open-label pilot study evaluating by magnetic resonance imaging the potential for a disease-modifying effect of celecoxib compared to a modelized historical control cohort in the treatment of knee osteoarthritis. Semin Arthritis Rheum. 2010 Dec; 40(3): 185-192.
[2] Trelle S et coll. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011; 342: c7086

The authors concluded that none of the molecules studied was free from an undesirable cardiovascular effect.

Concerning the primary endpoint, compared to placebo, rofecoxib was the molecule that exposed the patient to the greatest risk of myocardial infarction (RR = 2.12 95% CI [1.26 – 3.56]). Naproxen was associated with the lowest cardiovascular risk for patients with osteoarthritis, a finding that the authors, however, weighed up against the digestive toxicity of this medicinal product. No significant difference was revealed in terms of an increased risk of myocardial infarction between etoricoxib and placebo: RR = 0.75 95% CI [0.23 - 2.39], or between celecoxib and placebo: RR = 1.35 95% CI [0.71 - 2.72].

As regards the secondary endpoint, CV mortality, etoricoxib and diclofenac were associated with the highest risk, statistically higher than placebo (etoricoxib: RR = 4.07 95% CI [1.23 - 15.7] and diclofenac: RR = 3.98 95% CI [1.48 - 12.7]), whilst celecoxib was not associated with a statistically significant increase in the risk of CV mortality compared to placebo (RR = 2.07 95% CI [0.98 - 4.55]).

Concerning the increased risk of stroke, ibuprofen has been associated with the highest risk: 3.36 95% CI [1.00 - 11.6]. A significant increase in the risk of stroke was also noted with diclofenac (2.86 95% CI [1.09 - 8.36]. Celecoxib and etoricoxib were not associated with a statistically significant increase in the risk compared to placebo (etoricoxib: 2.67 95% CI [0.82 - 8.72] and celecoxib: 1.12 95% CI [0.60 - 2.06]).

Some methodological limits of this meta-analysis were noted by the authors, particularly:

- the non-exhaustiveness of the tolerance data taken into account in particular, the Merck laboratory (using the ARCOXIA proprietary medicinal products) did not agree to provide them with the unpublished data on tolerance for etoricoxib and rofecoxib. The unpublished data of celecoxib and lumiracoxib were provided by the laboratories concerned.
- in some studies, there was no independent committee validating the adverse cardiovascular events. An analysis limited to the studies having this committee was carried out.
- the small number of events reported in the studies included in the meta-analysis, which caused inaccuracies in the analyses.

The additional bibliographical search identified a systematic review of the literature[3] relating to the cardiovascular risks associated with NSAIDs published in PLoS Medicine in September 2011.
This systematic review of the controlled observational studies included 30 case-control studies (184,946 cardiovascular events) and 21 cohort studies (involving 2.7 million people exposed to NSAIDs).

Of the NSAIDs most studied (evaluated in more than 10 studies), the highest cardiovascular risks were observed with rofecoxib (relative risk of 1.45 95% CI [1.33; 1.59]) and diclofenac (1.40 95% CI [1.27 - 1.55]). The lowest relative risk was observed with ibuprofen (1.18 95% CI [1.11 - 1.25] and naproxen, 1.09 95% CI [1.02 - 1.16]).
A statistically significant increase in cardiovascular risk was also noted with celecoxib, 1.17 95% CI [1.08 - 1.27].
For the NSAIDs that had fewer studies, the highest risks were observed with etoricoxib 2.05 95% CI [1.45 - 2.88], etodolac 1.55 95% CI [1.28 - 1.87] and indomethacine 1.30 95% CI [1.19 - 1.41].

[3] McGettigan P, Henry D (2011) Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. PLoS Med 8(9): e1001098. doi:10.1371/journal.pmed.1001098

A comparison between NSAIDs showed that etoricoxib has been associated with a higher cardiovascular risk than ibuprofen, RR = 1.68 99% CI [1.14 - 2.49], and naproxen, RR = 1.75 99% CI [1.16 - 2.64].
No difference was revealed between etodolac and naproxen and ibuprofen.

Some limitations were noted by the authors:

- the inclusion of observational studies involving methodological limitations
- evidence of heterogeneity during the analyses

4.3. Status in other countries

Celecoxib was authorised for the first time on 31 December 1998 in the United States. Since then, it has obtained a Marketing Authorisation in 127 countries and is currently marketed in 121 countries.

4.4. Conclusion

Since the last assessment of CELEBREX by the Transparency Committee on 10 December 2010, no new relevant data on efficacy have been submitted by the applicant or found in the literature.

Concerning tolerance, a meta-analysis carried out on the basis of the clinical trials and a systematic review of the literature on the basis of controlled observational studies were published in 2011 and confirmed, taking full account of their methodological limitations, that NSAIDs were associated with increased cardiovascular risk (myocardial infarction, stroke, CV mortality, etc.).
In the meta-analysis carried out on clinical trials,[2] etoricoxib (60 and 90 mg) was associated with a higher risk of CV mortality (secondary criterion) compared to placebo (RR = 4.07 95% CI [1.23 - 15.7]), of the same order as that of diclofenac 150 mg/daily (RR = 3.98 95% CI [1.48 - 12.7]). No statistically significant increase in the risk of CV mortality associated with celecoxib was found (200 to 400 mg/daily): RR = 2.07 95% CI [0.98 - 4.55]. In this meta-analysis, no statistically significant increase in the risk of stroke and myocardial infarction associated with etoricoxib or celecoxib compared to placebo was found.
In the systematic review of the literature carried out on observational studies,[3] a statistically significant increase in cardiovascular risk was observed with all of the NSAIDs studied: celecoxib (RR = 1.17 95% CI [1.08 - 1.27], etoricoxib (RR = 2.05 95% CI [1.45 - 2.88], diclofenac (1.40 95% CI [1.27 - 1.55], ibuprofen (1.18 95% CI [1.11 - 1.25], naproxen, 1.09 95% CI [1.02 - 1.16]).

Amendments are in progress to add "pulmonary embolism" and "chest pain" to the undesirable effects section of the SPC.

A re-assessment of the cardiovascular risk of all of the NSAIDs is under way at the EMA.

5 DRUG USAGE DATA

IMS-EPPM database (permanent study of the medical prescription), August 2011
728,000 prescriptions have been written for CELEBREX proprietary medicinal products. The average dosage was 1.2 tablets daily and the average prescription duration was 32.8 days.

GERS data
According to the GERS data (MAT (Moving Annual Total) end of January 2011), 1,700,975 boxes of CELEBREX® were sold between January 2010 and January 2011.

Table 2. Unit sales of CELEBREX over the last 3 years (GERS, MAT January 2011).

Presentation	02/2011	01/2010	01/2009
CELEBREX 100 mg hard capsules box of 30	197,367	186,873	176,351
CELEBREX 200 mg hard capsules box of 30	1,503,608	1,588,197	1,648,273
Total	1,700,975	1,775,070	1,824,624

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of the actual benefit

The Transparency Committee considers that the data available are unlikely to modify the previous assessment:

Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis are chronic disabling diseases.

These proprietary medicinal products are symptomatic treatments.

Their efficacy/adverse effects ratio is:
- moderate in osteoarthritis
- high in rheumatoid arthritis and ankylosing spondylitis.

Public health benefit
Osteoarthritis, rheumatoid arthritis and spondylitis are frequent serious chronic diseases constituting a major cause of invalidity. They are responsible for a marked reduction in quality of life and their psychological impact is considerable.
Their economic consequences are substantial not only because of the consumption of care that they engender but also the loss of working days that they cause.
In 2009, osteoarticular diseases (rheumatoid arthritis, ankylosing spondylitis, and severe scoliosis) represented the sixth most frequent cause of new admissions to long-term conditions, i.e. around 30,000 long-term conditions.[4]
In terms of public health, the burden caused by osteoarthritis, rheumatoid arthritis and spondylitis is therefore major.

Reduction of the functional limitations and incapacities caused by rheumatoid arthritis, spondylarthropathies and osteoarthritis, as well as improvement of the quality of life of

[4] The state of health of the population in France. Monitoring the aims annexed to the Law on Public Health. Report 2011. Research Department on Evaluation and Statistics Studies.

the people affected by chronic diseases, constitute a public health need that is consistent with established priorities (objectives nos. 83, 84, 85 and 87 of the Law of 9 August 2004 on public health policy, Plan on improvement of the quality of life of patients affected by chronic diseases 2007-2011).

The new data do not allow to conclude that CELEBREX has an additional impact in terms of morbidity and quality of life. In the same way as other conventional NSAIDs, it helps meet the identified public health requirement.

The proprietary medicinal product CELEBREX therefore has no recognised public health benefit compared to conventional NSAIDs.

CELEBREX, like all NSAIDs, is:

- a first-line medicine in the treatment of rheumatoid arthritis and ankylosing spondylitis and,
- a second-line medicine in the treatment of osteoarthritis.

There are numerous treatment alternatives: all of the NSAIDs (except for pyrazoles).

The actual benefit of these proprietary medicinal products remains substantial in the MA indications, whilst awaiting the conclusions of the EMA's re-assessment of the cardiovascular risk of all of the NSAIDs.

6.2. Re-assessment of improvement in actual benefit

The Transparency Committee considers that the data available are unlikely to modify the level of improvement in actual benefit of CELEBREX, i.e.: "CELEBREX does not provide any improvement in actual benefit (V) compared to other NSAIDs."

6.3. Transparency Committee recommendations

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosages in the Marketing Authorisation.

6.3.1. Packaging: Appropriate for the prescription conditions.

6.3.2. Reimbursement rate: 65%.