HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 December 2010

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 revision: 4 January 2010 (updating of the special warnings and adverse effects relating, in particular, to the serious hepatic reactions reported with celecoxib)

Reason for request: Re-assessment of the improvement in actual benefit at the company's request following the submission of new data, in accordance with article R.163-12 of the Social Security Code.

Medical, Economic and Public Health Assessment Division

CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Celecoxib

1.2. Indications

“Symptomatic relief in the treatment of osteoarthritis, rheumatoid polyarthritis 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 dose should be prescribed. The patient's need for symptomatic relief and therapeutic efficacy 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 polyarthritis
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 400 mg 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.”

1.4. Special groups

"Elderly (> 65 years)

As with every patient, 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 patients 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 to moderate renal impairment is limited, therefore such patients should be treated with caution.

Children

Celecoxib is not indicated for use in children.

Pregnant women

No clinical data on exposed pregnancies are available for celecoxib. Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations.
The potential for human risk in pregnancy is unknown, but cannot be excluded. Celecoxib, like other medicines inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester of pregnancy. Celecoxib is contraindicated in pregnancy and in women who can become pregnant. If a woman becomes pregnant during treatment, celecoxib should be discontinued.

Lactation

Women who take celecoxib should not breastfeed.

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, see the SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

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

2.2. Medicines in the same therapeutic category

Other non-steroidal anti inflammatory drugs indicated for the symptomatic treatment of osteoarthritis, rheumatoid polyarthritis (RA), and ankylosing spondylitis (AS).

2.3. Medicines with a similar therapeutic aim

Other symptomatic treatments with an immediate action, namely all non-antiinflammatory analgesics indicated for non-cancer-related chronic pain.

3 REMINDER OF THE COMMITTEE'S OPINIONS

Table 1: History of the levels of actual benefit (AB) and improvement in actual benefit (IAB) ascribed to celecoxib

Date of opinion	Request	AB	IAB
11 October 2000	**Inclusion** on the list of medicines reimbursed by National Health Insurance and approved for hospital use in osteoarthritis and RA	Substantial	**IAB III** A trial versus NSAID + antisecretory agent or versus NSAID + misoprostol would have allowed a better assessment of benefit in terms of the gastrointestinal tolerance of this new NSAID. This proprietary medicinal product provides a moderate, level III IAB in terms of tolerance in comparison with NSAIDs other than pyrazole NSAIDs.
16 June 2004	**Re-assessment** following the joint request of the Direction de la Sécurité Sociale [Social Security Department] and the Direction Générale de la Santé [General Department of Health] in 2002 and following the re-assessment of coxibs by the CPMP (EMEA, February 2004).	Substantial	**IAB IV** The analysis of the available results shows that the superior gastrointestinal tolerance of CELEBREX compared to COX-1 inhibitor NSAIDs is minimal according to the current data and level of evidence submitted. There was not found to be any notable cardiovasculardifference compared to NSAIDs. Consequently, given the superior gastrointestinal tolerance, this proprietary medicinal product provides a minor IAB (level IV) in comparison with conventional NSAIDs.
9 May 2007	**Renewal of inclusion** on the list of medicines reimbursed by National Health Insurance	Substantial	**IAB V** In view of the available data which do not provide categorical proof of superior gastrointestinal tolerance in terms of serious complications for celecoxib in comparison with non-selective NSAIDs, particularly in at-risk patients, and in view of a cardiovascular risk that has been the subject of recent changes to the SPC by the EMEA, the Transparency Committee considers that this proprietary medicinal product does not provide an IAB (V) in comparison with non-selective NSAIDs.
21 October 2009	**Inclusion** in the extension of indication ankylosing spondylitis	Substantial	**IAB V** In the treatment of ankylosing spondylitis, CELEBREX does not provide an IAB (V) in comparison with other NSAIDs.

4 UPDATE OF AVAILABLE DATA

4.1. Efficacy

To recap, in its opinion of 9 May 2007, the Transparency Committee lowered the level of IAB for CELEBREX in the treatment of rheumatoid arthritis and osteoarthritis from IV to V on the following grounds:

- "in view of the available data which do not provide categorical proof of superior gastrointestinal tolerance in terms of serious complications for celecoxib in comparison with non-selective NSAIDs, particularly in at-risk patients, and
- in view of a cardiovascular risk that has been the subject of recent changes to the SPC by the EMA,

the Transparency Committee considers that this proprietary medicinal product does not bring an IAB (V) in comparison with non-selective NSAIDs."

Furthermore, the Committee did not ascribe an IAB to CELEBREX on its inclusion for ankylosing spondylitis in October 2009.

The purpose of this dossier is a re-assessment of the level of IAB for CELEBREX in its three indications. The dossier is based mainly on data on gastrointestinal tolerance, in particular the results of a new clinical study comparing the gastrointestinal tolerance of celecoxib with that of the combination diclofenac + PPI (CONDOR[1] study). 6 publications (clinical and observational studies and reviews of the literature) from the literature search carried out by the company since May 2007, the date of the last opinion on the renewal of inclusion of CELEBREX, have also been added to the dossier.
No new study specifically evaluating the cardiovascular tolerance of CELEBREX has been supplied.

4.1.1. New clinical study: CONDOR[2]

This controlled, randomised, double-blind study ran from 31 October 2005 to 11 May 2009. Its main aim was to demonstrate that 6 months treatment with celecoxib (200 mg twice daily) is superior to a combination of sustained-release diclofenac (75 mg twice daily) and omeprazole (20 mg daily) in respect of the incidence of clinically significant upper and lower gastrointestinal events in patients with osteoarthritis and/or rheumatoid arthritis.

The following were included:

- patients aged 60 years or over with or without a history of gastroduodenal ulcers,
- or patients over 18 years of age with clinical symptoms of gastroduodenal ulcer within 90 days or more prior to the visit,
- patients who tested negative for *H. pylori*.

1 Celecoxib vs Omeprazole and Diclofenac for at-risk Osteoarthritis and Rheumatoid arthritis patients
2 Chan et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. The Lancet, Early Online Publication, 17 June 2010.

Among those not included were patients:
- with a bleeding gastrointestinal ulcer or an active gastrointestinal ulcer within 90 days of the selection visit,
- with a history of gastric or duodenal surgery other than surgical or laparoscopic treatment for gastroduodenal ulcer,
- recommended to continue PPI therapy (e.g.: recurring complications of ulcers, severe gastro-oesophageal reflux),
- treated with anticoagulants, including low-dose aspirin, other platelet inhibitors (ticlodipine, clopidrogel, dipyridamole),
- who, according to the investigator, require low-dose aspirin for cardiovascular prophylaxis but who have not yet been treated,
- with a suspected or confirmed diagnosis of inflammatory bowel disease,
- with erosive oesophagitis or gastric stenosis,
- with anaemia with a haemoglobin level < 11.5 g/dl,
- with an established history of ischaemic heart disease (stable angina, unstable angina, etc.), arteriopathy and/or cerebrovascular disease,
- with congestive heart failure.

The primary efficacy endpoint was a composite endpoint: Clinically Significant Upper and/or Lower GI Events (CSULGIE) at 6 months. It measured the incidence of clinically significant upper and lower gastrointestinal events.

The CSULGIE endpoint consisted of the following:
- gastroduodenal haemorrhage,
- large bowel haemorrhage,
- small bowel haemorrhage,
- acute gastrointestinal haemorrhage of unknown origin (including possible small bowel haemorrhage),
- perforation of any part of the gastrointestinal tract,
- a clinically significant decrease in haemoglobin determined as being of gastrointestinal origin, such as a drop of ≥ 10% in haematocrit and ≥ 2 g/dl in haemoglobin,
- a clinically significant decrease in haemoglobin (defined as a drop of ≥ 2 g/dl in haemoglobin and/or a drop of ≥ 10% in haematocrit) of presumed gastrointestinal origin (including possible small bowel blood loss),
- gastric stenosis.

An independent committee consisting of 4 gastroenterologists was set up to check blind, for each patient with haematemesis, melaena, or any other type of gastrointestinal event (obstruction, perforation, bleeding), whether this event could be classified as being covered by the CSULGIE endpoint.

Results:

Characteristics of the patients included:
In total, 4460 patients were included and randomised to receive:
- celecoxib 200 mg twice daily, n = 2223,
  or
- diclofenac SR 75 mg twice daily + omeprazole 20 mg/day, n = 2237.

The mean age of the patients was 65 years (65.2 [26-89] years in the celecoxib group versus 65.3 [25-93] years in the diclofenac + omeprazole group). Less than 18% of the patients had a history of gastroduodenal ulcer.

The proportion of patients aged 65 years or over was 54.4% in the celecoxib arm and 54.7% in the diclofenac + PPI arm.

Results for the primary endpoint:
A statistically significant difference in favour of celecoxib was found on the primary endpoint: 20 out of 2238 patients (0.9%) in the celecoxib group and 81 out of 2246 patients (3.6%) in the diclofenac + omeprazole group were deemed by the independent committee as having had an upper or lower gastrointestinal event (CSULGIE), $p < 0.0001$. The difference observed on the composite endpoint is mainly attributable to the decrease in haemoglobin.

Table 2: CSULGIE score - ITT population

ITT population	*Number of patients (%)*	
	Celecoxib (200 mg 2x/day) N = 2238 n (%)	Diclofenac SR (75 mg x2/day) + omeprazole (20 mg/day) N = 2246 n (%)
CSULGIE score n (%)	20 (0.9)	81 (3.6)
	p < 0.0001	
Gastroduodenal haemorrhage	3 (0.1)	3 (0.1)
Gastric obstruction	0	0
Perforation of any part of the gastrointestinal tract	0	0
Large bowel haemorrhage	1 (<0.1)	1 (<0.1)
Small bowel haemorrhage	0	0
Acute gastrointestinal haemorrhage of unknown origin	1 (<0.1)	0
Clinically significant decrease in haemoglobin (≥ 2 g/dl) or haematocrit (≥ 10%) of confirmed gastrointestinal origin, - gastroduodenal ulcer/erosion - stomach cancer at an early age - lower gastrointestinal tract bleeding - lower gastrointestinal tract ulcer/erosion	5 (0.2) 5 0 0 0	24 (1.1) 20 1 1 2
Clinically significant decrease in haemoglobin (≥ 2 g/dl) or haematocrit (≥ 10%) of presumed gastrointestinal origin	10 (0.4)	53 (2.3)

The proportion of patients who dropped out of the study because of gastrointestinal adverse events (secondary endpoint) was higher in the diclofenac + omeprazole group (7.4%) than in the celecoxib group (5.1%); $p < 0.0006$.

No difference was demonstrated between the 2 groups as regards treatment-related severe adverse effects[3]: 38 (1.7%) in the celecoxib group versus 44 (2%) in the diclofenac + PPI group. The proportion of patients with moderate to severe abdominal symptoms was 15% with celecoxib and 17.1% with diclofenac + PPI.

In total, there were 2 deaths in the celecoxib group and 4 in the diclofenac + PPI group. One death in each group was considered to be treatment-related (pulmonary embolism and cardiogenic shock in the celecoxib group, cause not specified in the diclofenac + PPI group).

The results of the CONDOR study are hard to interpret given that the selected primary endpoint is a new composite endpoint of debatable validity and that the difference observed is attributable mainly to a surrogate endpoint: a decrease in haemoglobin.

3 not defined

4.1.2. Review of the literature

The company cites the following data from two new clinical studies.

Study by Goldstein et al 2007[4]
This controlled, randomised, double-blind study compared the incidence of gastroduodenal ulcers at 12 weeks in patients treated with celecoxib 200 mg/day and patients treated with a combination of naproxen 500 mg twice daily plus lansoprazole 30 mg once daily. The study included 1045 patients with osteoarthritis, who were treated with low-dose aspirin (prescribed on an open basis at a dosage of 81 or 325 mg/day).
No difference was demonstrated between the two groups: the proportion of patients with an endoscopically confirmed gastroduodenal ulcer at week 12 (or at the last visit in the case of premature discontinuation) was 9.9% with celecoxib and 8.9% with the fixed combination.

However, the non-inclusion criteria included history of gastroduodenal ulcer or of gastrointestinal haemorrhage, which means that the results of this study cannot be extrapolated to a population at high gastrointestinal risk. In addition, the value of the results is limited by the fact that the analysis was not carried out on an ITT basis (randomised population, n = 1045) but on the basis of the population that had undergone endoscopy at the initial and final visits, i.e. 854 patients. Furthermore, one of the major limitations of this study is the endoscopic primary endpoint, the validity of which is controversial, particularly in the population of patients treated with low-dose aspirin, as aspirin is a platelet aggregation inhibitor.

Study by Dahlberg et al 2009[5]
This controlled, randomised, double-blind study compared the percentages of patients discontinuing treatment because of adverse events in a group treated with celecoxib 200 mg once daily for a year and another treated with diclofenac 50 mg twice daily for a year. 925 patients (randomised population) aged 60 years or over with osteoarthritis of the knee or hip were included in the study.
The analysis of the results was carried out on a modified ITT basis, i.e. on the basis of the population of patients who had received at least one dose of treatment, or 916 patients.
No statistical difference was demonstrated between the 2 groups: the proportion of patients discontinuing treatment because of adverse events was 27% with celecoxib and 31% with diclofenac. The most frequent reason for discontinuation of treatment was gastrointestinal tolerance: 68 gastrointestinal events in the celecoxib group versus 66 in the diclofenac group.

Two reviews of the literature were analysed.

Review by Chen et al 2008[6]
The aim of this literature review was to evaluate the efficacy and cost-effectiveness of coxibs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) in the treatment of osteoarthritis or rheumatoid arthritis. Only the efficacy results for celecoxib will be presented.
Fourteen (14) randomised studies that compared celecoxib 200-800 mg/day with placebo or with certain traditional NSAIDs (diclofenac, ibuprofen, naproxen) were included in this analysis. There were fewer symptomatic gastrointestinal events (RR = 0.55, 95% CI: [0.40; 0.76] and fewer complicated gastrointestinal events (RR = 0.57, 95% CI: [0.35; 0.95] with celecoxib than with the other NSAIDs.

4 Goldstein J.L et al. Celecoxib plus aspirin versus naproxen and lansoprazole plus aspirin: a randomized, double-blind, endoscopic trial. Clin Gastroenterol Hepatol, 2007; 5: 1167-74.
5 Dahlberg L.E. et al. A randomized, multicentre, double-blind, parallel-group study to assess the adverse event-related discontinuation rate with celecoxib and diclofenac in elderly patients with osteoarthritis. Scand J Rheumatol, 2009; 38: 133-43.
6 Chen, Y.F. et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. HTA 2008; 12(11): PAGES MISSING

The risk of myocardial infarct appeared to be higher with celecoxib (RR = 1.77, 95% CI: [1.00; 3.11]. The dosage of the traditional NSAIDs that was used in the studies was not documented.

Review by Rostom et al 2007[7]
The aim of this Cochrane systematic literature review was to evaluate the upper gastrointestinal tolerance of coxibs (celecoxib, rofecoxib, etoricoxib, meloxicam, valdecoxib, and lumiracoxib) in comparison with that of the other NSAIDs and placebo in osteoarthritis patients over 18 years of age.
Sixty nine (69) clinical studies were included in this analysis. Only the efficacy results for celecoxib are presented.
There were fewer gastroduodenal ulcers (detected by endoscopy): RR = 0.21, 95% CI: [0.16-0.28] (5 studies; N = 2439) and fewer ulcer complications: 0.23, 95% CI: [0.07-0.76] (4 studies; N = 31,106 patients) with celecoxib than with the non-selective NSAIDs.
However, subgroup analyses in patients treated concomitantly with aspirin did not show any statistically significant difference in regard to ulcer complications: RR = 0.89, 95% CI: [0.52; 1.53] between coxibs and non-selective NSAIDs (4 studies, 2 of which were carried out with celecoxib, approximately 7000 patients).

4.1.3. Two observational studies

Laharie et al 2010[8]
This is a publication on the CADEUS observational study which has already been examined by the Transparency Committee. It was carried out in 46,454 patients and analysed the number of hospital admissions due to gastrointestinal or cardiovascular events observed during real-life use of NSAIDs. There were 12 hospital admissions due to gastrointestinal events with coxibs versus 9 with other NSAIDs, there being no statistical difference between the groups. There were 13 hospital admissions due to gastrointestinal events with coxibs versus 8 with other NSAIDs, there being no statistical difference between the groups.

Van der Linden et al. 2009[9]
The aim of this Danish cohort study was to compare rates of hospitalisation due to upper and lower gastrointestinal events between chronic (more than 60 days' prescription in the first year) and acute users of traditional NSAIDs combined with a PPI and users of coxibs. This study was carried out between 1 January 2000 and 31 December 2004 using a Danish database of 3 million people.
A total of 597,190 new users of NSAIDs, defined as patients who had not been treated with NSAIDs in the 6 months leading up to this study, were included. Over 90% of them used NSAIDs for short-term therapy. They had to have a ≥ 1-year history in the database prior to administration of their 1st NSAID and had to have been followed up for ≥ 1 year after their 1st admission to hospital for a gastrointestinal event.
In the cohort, 544,210 patients were treated with traditional NSAIDs only, 23,999 with traditional NSAIDs + PPI, 25,977 with coxibs, and 3004 with coxibs + PPI.

The mean age was 43.9 ± 17.2 years in the traditional NSAIDs only group, 58.1 ± 15.5 years in the traditional NSAIDs + PPI group, 56.7 ± 17.5 years in the coxibs group, and 63.7 ± 14.1 years in the coxibs + PPI group.

7 Rostom, A. et al. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. Clin Gastroenterol Hepatol, 2007; 5 : 818-28.
8 Laharie D et al. Hospitalizations for gastrointestinal and cardiovascular events in the CADEUS cohort of traditional or Coxib NSAID users. Br J Clin Pharmacol, 2010; 69 : 295-302.
9 Van der Linden et al. COX-2 inhibitors: complex association with lower risk of hospitalization for gastrointestinal events compared to traditional NSAIDs plus proton pump inhibitors. Pharmacoepidemiol Drug Saf 2009; 18: 880-90.

In the acute users of NSAIDs there was found to be:
- less of a risk of hospitalisation for upper gastrointestinal events (RR: 0.21, 95% CI: [0.16; 0.28]) and lower gastrointestinal events (RR: 0.26, 95% CI: [0.16; 0.42]) with coxibs on their own than with traditional NSAIDs + PPI;
- less risk of hospitalisation for upper gastrointestinal events with traditional NSAIDs on their own than with traditional NSAIDs + PPI (RR: 0.26, 95% CI: [0.18; 0.37]) and less risk of hospitalisation for lower gastrointestinal events (RR: 0.25, 95% CI: [0.16; 0.39]);
- no statistical difference in the percentage of patients hospitalised for upper and lower gastrointestinal events between the patients given coxib + PPI therapy and those given NSAID + PPI therapy.

In the chronic users there was found to be:
- less risk of hospitalisation for upper gastrointestinal events (RR: 0.35, 95% CI: [0.22; 0.55]) and lower gastrointestinal events (RR: 0.43, 95% CI: [0.25; 0.75]) with coxibs on their own than with traditional NSAIDs + PPI;
- less risk of hospitalisation for upper gastrointestinal events (RR: 0.41, 95% CI: [0.27; 0.62]) and lower gastrointestinal events (RR: 0.43, 95% CI: [0.26; 0.72]) with traditional NSAIDs on their own than with non-selective NSAIDs + PPI;
- no statistically significant difference between coxibs + PPI and traditional NSAIDs + PPI.

The results of this observational study must be interpreted with caution.

In addition, the company submitted the results of a Canadian retrospective observational study[10] which compared the percentage rates of hospitalisation for upper and lower gastrointestinal events associated with non-selective NSAIDs and paracetamol. As celecoxib was not included in this study, the results are not described.

4.2. Adverse effects

The dossier submitted provides new data on the gastrointestinal tolerance of celecoxib, but no study specifically evaluating its cardiovascular tolerance has been supplied. Changes to the SPC have occurred since the last opinion on CELEBREX in October 2009 and are as follows:

4.4. Special warnings and special precautions for use

Addition of:

Some cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis, and hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib. Among the cases that reported time to onset, most of the severe hepatic reactions were developed within one month after initiation of treatment.

4.8 Undesirable effects

Replacement of: "Hepatitis, jaundice, hepatic failure"
by: "Hepatic failure (sometimes with fatal outcome or requiring liver transplant), fulminant hepatitis (sometimes fatal), liver necrosis, hepatitis, jaundice"

10 Rahme E et al. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. Am J Gastroenterol 2008; 103: 872-82.

4.3. Conclusion

In its last opinion on the renewal of inclusion of the proprietary medicinal product CELEBREX (celecoxib) dated 9 May 2007, the Transparency Committee considered that “this proprietary medicinal product did not bring an IAB (V) in comparison with non-selective NSAIDs in view of its cardiovascular risk and the absence of categorical proof of its superior gastrointestinal tolerance in terms of serious complications in comparison with non-selective NSAIDs, particularly in at-risk patients”.
In addition, in its opinion of 21 October 2009 concerning the inclusion of CELEBREX in the extension of indication ‘ankylosing spondylitis’, the Transparency Committee did not ascribe it an IAB.

On the basis of the results of a new clinical study (CONDOR) which evaluated the gastrointestinal tolerance of celecoxib, the company requested a review of the level of improvement in actual benefit afforded by this medicine.

In this study, celecoxib (200 mg twice daily) was compared with a combination of sustained-release diclofenac (75 mg twice daily) and omeprazole (20 mg per day) in respect of the incidence of clinically significant upper and lower gastrointestinal events in patients with osteoarthritis and/or rheumatoid arthritis who were aged 60 years or over, with or without history of gastroduodenal ulcers; or patients who were over 18 years of age and had clinical symptoms of gastroduodenal ulcer within 90 days or more prior to the visit.
The primary efficacy endpoint was a composite one: Clinically Significant Upper and/or Lower GI Events (CSULGIE). It measured the incidence of upper and lower gastrointestinal events.
A statistically significant difference in favour of celecoxib was found: 20 out of 2238 patients (0.9%) in the celecoxib group and 81 out of 2246 patients (3.6%) in the diclofenac + omeprazole group were deemed by the independent committee as having had an upper or lower gastrointestinal event (CSULGIE), $p < 0.0001$. However, the difference observed on the composite endpoint is mainly attributable to a surrogate endpoint: the decrease in haemoglobin.

The SPC now mentions cases of severe hepatic reactions, including fulminant hepatitis (in some instances with a fatal outcome), liver necrosis, and hepatic failure (in some instances with a fatal outcome or requiring liver transplant).

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Re-assessment of actual benefit

Rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis are disabling chronic 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

The public health burden of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, which are severe and disabling chronic diseases, is considerable .

Improving the therapeutic management of these diseases is a public-health need that is one of the objectives of the GTNDO[11] and the plan to improve the quality of life of people with chronic diseases for 2007-2011.

On the basis of the available new data, CELEBREX does not have an impact on morbidity and patients' quality of life. Nevertheless, like the other NSAIDs, CELEBREX helps to meet the identified need.

Consequently, in the current state of knowledge and in view of the other therapies available, the non-ascription of a public health benefit to CELEBREX in ankylosing spondylitis in 2009 is confirmed in all of its indications.

CELEBREX, like all NSAIDs, is a:
- first-line medicine in the treatment of rheumatoid arthritis and ankylosing spondylitis, and
- second-line medicine in osteoarthritis.

There are numerous treatment alternatives: all NSAIDs (apart from the pyrazoles).

The actual benefit of these proprietary medicinal products remains substantial in the Marketing Authorisation indications.

5.2. Re-assessment of the improvement in actual benefit (IAB)

The Transparency Committee considers that the new data submitted, in particular the results of the CONDOR study, do not warrant a change to the level of improvement in actual benefit ascribed to CELEBREX in osteoarthritis and rheumatoid arthritis on 9 May 2007 and in ankylosing spondylitis on 21 October 2009, namely: "CELEBREX does not bring an improvement in actual benefit (V) in comparison with other NSAIDs".

11 GTNDO: Groupe Technique National de Définition des Objectifs [National technical group for the setting of public-health objectives] (DGS [Ministry of Health]) 2003