HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 January 2012

ARCOXIA 30 mg, film-coated tablet
B/28 (CIP code: 387 980-8)
B/98 (CIP code: 573 530-9)

ARCOXIA 60 mg, film-coated-tablet
B/28 (CIP code: 387 925-7)
B/50 (CIP code: 573 501-9)

Applicant: MSD - CHIBRET

etoricoxib
ATC code: M01AH05 (NSAID)

List I

Date of Marketing Authorisation: 28 August 2008 (mutual recognition procedure)

Reason for request: Re-assessment of the Actual Benefit at the request of the Transparency Committee in compliance with Article R 163-21 of the French Social Security Code.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

etoricoxib

1.2. Indication

"The symptomatic relief of osteoarthritis.
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

"ARCOXIA is administered orally and may be taken with or without food. When rapid symptomatic relief is needed, it should be noted that the efficacy of this medicinal product is greater if etoricoxib is administered without food.
As the cardiovascular risks of etoricoxib 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.
The recommended dose is 30 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 60 mg once daily may increase efficacy. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.
Doses greater than those recommended have either not demonstrated additional efficacy or have not been studied. Consequently, the dose for osteoarthritis should not exceed 60 mg daily."

Elderly: no dosage adjustment is necessary for elderly patients. As with other medicinal products, caution should be exercised in elderly patients.

Hepatic insufficiency: in patients with mild hepatic dysfunction (Child-Pugh score 5-6), a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7-9), a dose of 60 mg once every other day should not be exceeded; a dose of 30 mg once daily may also be considered.

Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There is no clinical experience in patients with severe hepatic dysfunction (Child-Pugh score $\geq$ 10); therefore, the use of this medicinal product is contraindicated in these patients.

Renal insufficiency: no dosage adjustment is necessary for patients with a creatinine clearance of $\geq$ 30 ml/min. The use of etoricoxib in patients with creatinine clearance <30 ml/min is contraindicated.

Paediatric patients: etoricoxib is contraindicated in children and adolescents under 16 years of age.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

M : Musculo-skeletal system
M01 : Antiinflammatory and antirheumatic products
M01A : Antiinflammatory and antirheumatic products, non-steroids
M01AH : Coxibs
M01AH05 : etoricoxib

2.2. Medicines in the same therapeutic category

These are all NSAIDs indicated in the symptomatic treatment of osteoarthritis.

2.3. Medicines with a similar therapeutic aim

These are all analgesics indicated in the symptomatic treatment of osteoarthritis.

3 ASSESSMENT CONTEXT

Re-assessment of selective COX-2 inhibitor anti-inflammatories (ARCOXIA 30 and 60 mg and CELEBREX 100 and 200 mg) was requested by the Transparency Committee due to tolerance concerns (cardiovascular, renal, cutaneous and gastrointestinal) linked to this class of medicinal products, in compliance with Article R 163-21 of the French Social Security Code.

It should be noted that on 29 April 2009 the Transparency Committee issued an opinion:

- recommending inclusion on the list of medicines refundable by National Health Insurance for ARCOXIA (etoricoxib) 30 mg and 60 mg for osteoarthritis;
- not recommending inclusion for the dosage at 120 mg for gout.

The request for inclusion for the 90 mg dosage for rheumatoid arthritis was withdrawn by the laboratory.

The data presented in April 2009 demonstrated that ARCOXIA at doses of 30 and 60 mg had a comparable efficacy for osteoarthritis with those of other NSAIDs, often though with a greater risk of arterial hypertension. The Actual Benefit (AB) of these medicinal products was qualified as being moderate and no Improvement in Actual Benefit (IAB) was seen from them compared with other NSAIDs.
Following this opinion, the proprietary medicinal products ARCOXIA were included in the Official Gazette on 26 February 2010, and have been marketed in France since 12 March 2010.

Within the scope of this re-assessment, the manufacturing laboratory has been asked to provide all available data since the previous assessment.
The following were provided:

- an update of efficacy and tolerance data from clinical studies;
- an update of pharmacovigilance data;
- usage data.

The HAS document research department has carried out an additional bibliographical review using the Medline, Embase and Cochrane databases.
The AFSSAPS pharmacovigilance department was contacted, and later provided the Clermont-Ferrand CRPV report.
Reimbursement data was requested from the Medical Insurance Funds. A search of the EGB database was carried out.

4 ANALYSIS OF AVAILABLE DATA

4.1. Efficacy

No new trial investigating the efficacy of etoricoxib for osteoarthritis has been provided by the laboratory. All that they have provided is the *per protocol* analyses of non-inferiority trials 018 and 019 versus naproxen and trial 805 versus diclofenac (without a placebo arm), the ITT analyses results of which were examined by the Committee within the scope of the inclusion on the list for reimbursement. These *per protocol* analyses confirm the results from the ITT analyses, showing the non-inferiority of etoricoxib 60 mg/day compared with naproxen 1000 mg and with diclofenac 150 mg/day. Non-inferiority was defined as a time-weighted average difference in response (etoricoxib – comparator) below the threshold of 10 mm on a VAS of 100 mm.

A review of the literature did not identify any new clinical studies of efficacy published since the last Transparency Committee opinion of 29 April 2009.

4.2. Adverse Effects

A summary of the previous Transparency Committee conclusions concerning the tolerance of ARCOXIA in April 2009:

"Gastrointestinal tolerance: upper gastrointestinal complications (perforations, ulcers or haemorrhages), some of which were fatal, were observed with etoricoxib. Despite the available data suggesting a better gastrointestinal tolerance with etoricoxib compared with non-selective NSAIDs taken at their maximum dosage and without gastroprotective medication, it should be noted that no difference was highlighted concerning complications in the MEDAL programme. Consequently, extreme care is recommended for populations at risk of gastrointestinal complications (the elderly, those with a previous history of ulcers or haemorrhages or those receiving concomitant treatment with aspirin, clopidogrel, anticoagulants or corticosteroids).

Cardiovascular tolerance: available data suggests that ARCOXIA causes an additional cardiovascular risk compared with other NSAIDs already marketed. In the MEDAL programme, renovascular effects (AHT, oedema, congestive heart failure) were more common with etoricoxib than with diclofenac, and these effects were dose-dependent (statistically significant for etoricoxib 90 mg but not for etoricoxib 60 mg). The SPC states that: "Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses."
Skin tolerance: the risk of serious skin reactions cannot be ruled out with etoricoxib."

Given the risks identified (thrombotic cardiovascular complications, gastrointestinal complications, cardio-renal risk, risk of skin reactions), particular attention was given to tolerance data within the scope of this re-assessment.

4.2.1. Data from clinical studies

Cardiovascular tolerance:

The laboratory was aware of the MEDAL programme and the MEDAL study, which were previously analysed in the Opinion of 29 April 2009. With regard to the MEDAL Programme, with the primary objective of evaluating the non-inferiority of etoricoxib (60 mg and 90 mg combined) compared with diclofenac 150 mg in the risk of thrombotic cardiovascular events

based on the combined results of three studies, it should be noted that it had "methodological limitations, making the interpretation of results difficult:
- the absence of a placebo arm,
- the absence of discussion regarding the choice of the threshold non-inferiority value,
- the absence of discussion regarding the differences between the trials, especially in terms of their objectives,
- the comparison of two doses of etoricoxib (medium - 60 mg and high dose - 90 mg) with diclofenac 150 mg (maximum authorised dose) was not relevant or it is recommended to use NSAIDs at their minimal effective dose for osteoarthritis."

In addition, this programme did not allow the risks linked to the use of 30 and 60 mg doses to be precisely evaluated in the osteoarthritic population (dose and indication used within the scope of reimbursement in France) given the:
- use of higher dosages (60 and 90 mg) in this programme;
- inclusion of patients with different conditions (osteoarthritis and rheumatoid arthritis)
- high inclination to prescribe aspirin at low doses and gastric protection medication, even if this is not always followed in current practice.

The laboratory provided a meta-analysis.[1]

This meta-analysis evaluated the cardiovascular effects of NSAIDs. The analysis included 31 trials, concerning 116,429 patients (MEDAL programme for etoricoxib versus diclofenac). Seven NSAIDs were investigated - naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib and lumiracoxib at a range of dosages and for various conditions.
The primary efficacy endpoint was the occurrence of a myocardial infarction.
The secondary endpoints included:
- death from a cardiovascular cause,
- cerebral vascular accident,
- death from any cause,
- death from an unknown cause.

The authors concluded that none of the molecules investigated were exempt from adverse cardiovascular effects. When it came to the primary efficacy endpoint, compared with the placebo, rofecoxib was the molecule that had 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, noting that the authors often weighed this up against the gastrointestinal toxicity of this medicinal product. No significant difference was highlighted in terms of an increase in the risk of myocardial infarction between etoricoxib and the placebo: RR = 0.75, 95% CI [0.23 - 2.39], or between celecoxib and the placebo: RR = 1.35, 95% CI [0.71 - 2.72].

For the secondary endpoint, death from a cardiovascular cause, etoricoxib and diclofenac were associated with a higher risk, statistically greater than the placebo (etoricoxib: RR = 4.07, 95% CI [1.23 - 15.7] and diclofenac: RR = 3.98 95% CI [1.48 - 12.7]) although celecoxib was not associated with a statistically significant increase in risk from a cardiovascular cause compared with placebo (RR = 2.07 95% CI [0.98 - 4.55]).

With regard to the increase in the risk of CVA, ibuprofen was associated with a higher risk: 3.36, 95% CI [1.00 - 11.6]. A significant increase in risk of CVA 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 CVA compared with placebo (etoricoxib: 2.67, 95% CI [0.82 - 8.72] and celecoxib: 1.12, 95% CI [0.60 - 2.06]).

1 Trelle S et coll. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086

Limitations in the methodology of this meta-analysis were revealed by the authors, especially:

- the incompleteness of tolerance data taken into account; the Merck laboratory (manufacturer of the proprietary medicinal products ARCOXIA) did not agree to provide non-published tolerance data for etoricoxib and rofecoxib. The non-published data for celecoxib and lumiracoxib was provided by the laboratories concerned.
- in certain studies, there was no independent board reviewing the adverse cardiovascular events. A limited analysis of those studies with a review board was conducted.
- the low number of events reported in the studies included in the meta-analysis that led to inaccuracies in the analyses.

No new studies specifically evaluating the incidence of AH and the risk of congestive heart failure with etoricoxib were included in the file. Only post-hoc analyses of the MEDAL programme, previously evaluated by The Transparency Committee in 2009, were provided.

The additional bibliographic investigation allowed a systematic review of the literature[2] to be identified, relating to the cardiovascular risks associated with NSAIDs published in PLOS Medicine in September 2011.
This systematic review of controlled, observational studies included 30 case-control studies (184,946 cardiovascular events) and 21 cohort studies (based on more than 2.7 million people exposed to NSAIDs).

For the most studied NSAIDs (evaluated in 10 studies or more), higher cardiovascular risks were observed for 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 for ibuprofen (1.18, 95% CI [1.11 - 1.25] and naproxen, 1.09, 95% CI [1.02 - 1.16]).
It was also noted that there was a statistically significant increase in cardiovascular risk for celecoxib: 1.17, 95% CI [1.08 - 1.27].
For the lesser studied NSAIDs, 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 indomethacin 1.30, 95% CI [1.19 - 1.41].
A comparison of NSAIDs showed that etoricoxib was 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].
There was no difference highlighted between etodolac and naproxen or ibuprofen.

Limitations were revealed by the authors:

- the inclusion of observational studies with methodological limitations
- the highlighting of heterogeneity during analyses

Gastrointestinal tolerance:

The laboratory provided the MEDAL programme results and a systematic Cochrane review of the upper gastrointestinal tolerance of coxibs (Rostom et al, published in 2007), which had been previously analysed by the Transparency Committee.

As a reminder, 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 those of the other NSAIDs and placebo in osteoarthritis patients over 18 years of age.
Sixty nine (69) clinical studies were included in this analysis. It highlighted fewer gastroduodenal ulcers (detected by endoscopy): RR = 0.26; 95% CI: [0.23 – 0.30] and fewer

2 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

ulcer complications: 0.39; 95% CI [0.31 – 0.50] with coxibs than with non-selective NSAIDs. However, subgroup analyses in patients treated concomitantly with aspirin did not show any statistically significant difference with regard to ulcer complications: RR = 0.89 95% CI: [0.52; 1.53] between coxibs and non-selective NSAIDs.

Regarding the MEDAL programme, the Committee noted in its previous opinion that: "no definitive conclusion can be drawn from this data, due to the fact that the gastrointestinal tolerance was only evaluated on an exploratory basis, and also that a significant percentage of patients in the 2 groups (etoricoxib and diclofenac) received a PPI. Indeed, the percentage of patients taking a PPI was 39% at the start in the 2 arms and 82% of patients on etoricoxib and on diclofenac took a PPI over a period of ≥ 75% of the duration of the trial.[3] As an indication, the confirmed rate of upper gastrointestinal clinical events (perforations, ulcers, haemorrhages) was significantly lower for etoricoxib (1.01%) than for diclofenac (1.42%), RR = 0.69, 95% CI [0.57- 0.83]. However, no difference was highlighted between etoricoxib and diclofenac on the rate of upper gastrointestinal events considered as being *"complicated**" (complicated perforations, obstructions and bleeds): 0.45% with etoricoxib versus 0.47% with diclofenac, NS.

Furthermore, no difference was highlighted between etoricoxib and diclofenac on the rate of confirmed lower gastrointestinal clinical events (perforations, obstructions, haemorrhages or PUH): 0.48% with etoricoxib versus 0.56% with diclofenac, RR =0.84, 95% CI [0.63-1.13]. Finally, no difference was highlighted between etoricoxib and diclofenac for upper gastrointestinal events for patients concomitantly taking low doses of aspirin (approximately 33% of patients) - data from SPC."

Additional bibliographic research carried out by the HAS documents department did not identify any other relevant data.

4.2.2. Pharmacovigilance data

French data

A supported national pharmacovigilance follow-up was referred to the regional pharmacovigilance centre (CRPV) in Clermont Ferrand by AFSSAPS. Between 12 March 2010 and 11 March 2011 (which was after one year of the marketing of ARCOXIA in France), 249 adverse events occuring in 150 patients resulted in a spontaneous notification. These were essentially in women (71%). The mean age was 63 ± 14 years; 103 cases (69%) of the adverse events were not serious and 47 cases (31%) were serious.
The serious cases involved:

- 26 admissions to hospital or extensions to a hospital stay,
- 4 life-threatening prognoses given,
- 14 other serious medical situations,
- 2 deaths, although it is unknown if they were due to ARCOXIA.

When evolution was known, serious cases mainly resulted in recovery with no ill effects (64%). The indication of etoricoxib, when it was stated, was mainly for osteoarthritis (55%). When the dosage was known, it was 30 mg/day in 54% of cases and 60 mg/day in 44%.

The most common adverse effects reported, and in order of decreasing frequency were: general disorders (19%), gastrointestinal conditions (14.5%), cardiac issues (14%), vascular problems (12%), skin disorders (8%), nervous system problems (7%) and respiratory, chest and interpulmonary issues (6.5%).

3The mean trial duration was 18 months.

Regarding the adverse effects that were of interest, these were:

- gastrointestinal events : 1 haematemesis, 3 gastrointestinal haemorrhages,
- 1 gastroduodenitis,
- thrombotic cardiovascular events: 2 MIs, 2 acute coronary syndromes and 2 CVAs,
- reno-vascular events: 28 cases of oedema, 6 heart failures or decompensation, 19 elevated blood pressures (mainly non-serious but 3 cases of hypertensive flare-ups with a BP > 180 mm Hg occurred), 3 acute renal failures,
- skin events and hypersensitivity: 1 Lyell syndrome, 1 Quincke's oedema,
- one exposed pregnancy, the outcome of which is unknown, was declared.

Misuse, apart from a breach in indication, was noted 13 times (9%), with non-consideration of cardiovascular risk factors in 5 cases and the taking of non recommended products in 5 cases (NSAIDs, diuretics), not following a contraindication (previous history of aspirin allergy), one case of a very high dose and one of an extended prescription period (7 months).

Regarding the adverse events of interest, especially gastrointestinal haemorrhages and thrombotic cardiovascular accidents, the analysis of spontaneous notifications did not allow their incidence to be evaluated due to under-notification.

An additional analysis, carried out by the CRPV on 9 December 2011, did not identify any new pharmacovigilance warnings. Cases of misuse concerned indication (n =78 cases, 27%, joint pain 10.5%, ankylosing spondylitis 3.8% and rheumatoid arthritis 1.7%) and cardiovascular risk factors (7 cases). The maximum dosage was respected.

In conclusion, the French national pharmacovigilance follow-up did not identify any new tolerance warnings for the identified risks of etoricoxib. However, 3 serious cases of nephrotic syndrome, for which the link to etoricoxib cannot be excluded, as well as 4 cases of venous thrombotic accidents, were reported. Furthermore, the indication did not appear to always be respected.

<u>International pharmacovigilance data</u>

Data from the last 3 PSURs were presented (periodic international pharmacovigilance report), the first covering the period from 1 April 2008 to 31 March 2009, the second, the period from 1 April 2009 to 31 March 2010 and the third the period from 1 April 2010 to 31 March 2011. The total number of patients exposed to ARCOXIA was estimated at 2,019,537 patients per year between 1 April 2008 and 31 march 2010 and 1,323,103 patients per year between 1 April 2010 and 31 March 2011. It should be noted that only the 30 and 60 mg doses are marketed and reimbursable in France; however, cases reported concern all ARCOXIA doses. No analysis of reported cases based on the doses prescribed or the average daily dose was provided.

A total of 1,262 adverse events, 512 of which were serious, were reported (including 34 deaths) between 1 April 2008 and 31 March 2010.

Among the 34 deaths reported between 1 April 2008 and 31 March 2010, these included:

- one foetal death (exposure during pregnancy with a spontaneous abortion),
- 9 cases linked to an adverse gastrointestinal event, of which 2 cases had a previous medical history and concomitant treatment including aspirin and ibuprofen,
- 1 case of fulminant hepatitis in association with ibuprofen in a 79-year-old patient,
- 9 cases linked to a cardiovascular event, 6 of which with co-morbidity factors including ischaemic heart disease, AH, diabetes, high blood cholesterol levels, atrial fibrillation, stomach cancer, etc.,
- 1 case of Stevens-Johnson syndrome in a 92-year-old patient,
- 1 case of hepatic insufficiency in a patient co-treated with tramadol,

- 6 cases, the information for which is missing.

During the period from 1 April 2010 to 31 March 2011, 9 deaths were reported. Due to co-morbidities, the advanced age of patients and concomitant treatments being administered, the link to etoricoxib for these deaths cannot be established.

Between 1 April 2008 and 31 March 2010, 60 cases of thrombotic cardiovascular events were reported, 27 of which were ischaemic CVAs, 35 heart disease and coronary infarctions and 8 were "other thromboembolic events," including pulmonary embolisms and deep vein thromboses.

Since the first date of marketing up to 30 September 2009, 144 renal insufficiency adverse events have been reported. Fourteen cases were fatal, which led to a change in the SPC: "renal insufficiency generally reversible upon stopping treatment" under "renal insufficiency".

Between 1 April 2008 and 31 March 2010, 605 perforations, ulcers and gastrointestinal haemorrhages were reported in patients with a mean age of 69 years. The patients had risk factors, including a previous history of ulcers (27.8%) and/or concomitant treatment favouring gastrointestinal complications (16%), mainly NSAIDs (10% of cases) aspirin, platelet aggregation inhibitors and/or anticoagulants.

Since its first marketing up to 31 March 2010, 274 skin reactions were reported, of which 56 were cases of Stevens-Johnson and Lyell syndromes. Patients were receiving concomitant treatment, such as other NSAIDs, including coxib, allopurinol and diuretics.

In conclusion, the analysis of international pharmacovigilance data covering the period from 1 April 2008 to 31 March 2011 did not identify any new tolerance warnings for the identified risks of etoricoxib at the validated dosages in France of 30 and 60 mg for osteoarthritis.

Amendments to the SPC introduced since 2009:
Following the Transparency Committee Opinion of 29 April 2009, the SPC for ARCOXIA has been amended to include new adverse effects.
Through a notification from AFSSAPS on 21 December 2009, "angina pectoris", "tachycardia" and "erythema" were added to section 4.8 Undesirable Effects of the SPC for etoricoxib, as well as "pancreatitis", "jaundice" and "serum creatinine increased".
Also added were: "Blood and lymphatic system disorders:
Uncommon: anaemia (primarily associated with gastro-intestinal bleeding), leukopenia, thrombocytopenia."

A type II variation was submitted at a European level on 12 May 2010, to include the undesirable effects "restlessness" and "arrhythmia" and to amend the wording of the undesirable effect "renal insufficiency generally reversible on stopping treatment " under "renal insufficiency", following the PSUR covering the period of 1 April 2008 to 31 March 2009. The French SPC is in the process of being updated. The laboratory also requested the addition, in the undesirable effects section, of the risk of hepatic insufficiency linked to treatment with etoricoxib, following a review of several cases implicating this medicinal product.

4.3. Usage data

Due to the possible increase in cardiovascular risks from etoricoxib with dose and treatment duration, the Transparency Committee has paid particular attention to the usage data of this medicinal product.

IMS Dorema (August 2011)
ARCOXIA proprietary medicinal products were the subject of 440,000 prescriptions, of which 270,000 concerned the 30 mg dose and 170,000 the 60 mg dose. The mean dose was 1 film-coated tablet per day and the mean prescription duration was 33.3 days.

Insurance fund data
Within the scope of this re-assessment, the Transparency Committee requested data concerning the reimbursement of these proprietary medicinal products

Data from the French National Health Insurance Fund (January 2011)

Number of boxes of ARCOXIA refundable, per format and per month

Periods	**30 mg, 28 film-coated tablets**	**60 mg, 28 film-coated tablets**
March-10	2,300	719
April-10	15,757	6,287
May-10	17,259	8,701
June-10	32,523	16,634
July-10	33,860	18,575
August-10	29,061	17,469
September-10	35,882	22,139
October-10	39,207	24,291
November-10	39,872	25,665
December-10	39,044	25,540
January-11	30,721	20,349
Cumulative total	315,486	186,369
EXTRAPOLATION FOR ALL PLANS	438,175	258,846

Official GERS Data (January 2011)

Period	ARCOXIA 30 mg, 28 film-coated tablets	ARCOXIA 60 mg, 28 film-coated tablets
GERS 01/2011	471,906	280,964

Health and retirement scheme for independent workers - RSI
Between the 1 February 2010 and 28 February 2011 (included for reimbursement on 27 February 2010), 20,230 insured parties were refundable at least once for the proprietary medicinal products ARCOXIA. These proprietary medicinal products were largely prescribed by general practitioners (75% of prescriptions). Rheumatologists issued 19% of prescriptions. The 30 mg dose was prescribed the most (61.6% of prescriptions).
During this period, a single box was refundable for 71.1% of patients; 139 people received 2 boxes at the 60 mg dose per prescription (of the 8,217 who received 60 mg during this period).

EGB data (general beneficiary sample)
Between 15 march 2010 and 29 August 2011, 4,123 patients subscribed to a general plan received reimbursement for at least one box of ARCOXIA 30 mg or 60 mg. Extrapolation of this data to the French population allows the number of users of ARCOXIA to be estimated at 547,905 (95% CI [531,238 – 564,573]. Reimbursements for the 30 mg format alone concerned 60% of the beneficiaries, the 60 mg format alone for 33% of beneficiaries and for both formats of 30 and 60 mg for 7% of beneficiaries.

Seventeen patients were identified as having been refundable for two boxes of ARCOXIA 60 mg on the same day.

Specific studies

Within the scope of the European RMP, 2 usage studies have been implemented:

- one study was carried out based on the data from the GPRD (General Practice Research Database)
- one case-control study that evaluated etoricoxib 90 mg in ankylosing spondylitis; the results have not been provided by the laboratory as this presentation is not marketed in France.

UK-GPRD Study (not published)

This retrospective, cohort study concerned the 60, 90 and 120 mg doses of etoricoxib (the 30 mg dose only obtained Marketing Authorisation in August 2007) and aimed to evaluate characteristics of patients treated and the true prescription conditions in general medicine in the United Kingdom. A total of 34,887 patients treated between 1 April 2002 and 31 December 2008 were included.

Before the implementation of risk minimisation measures (harmonisation of the SPC following the re-assessment of the risk/benefit ratio of the class by EMA with reinforcement of the precautions in February 2005), the patients treated had a mean age of 60.6 years versus 58.6 years after the introduction of these measures.

The proportion of at risk patients treated was not reduced: before and after the implementation of these measures, 29% of patients treated had arterial hypertension and 6% had a previous history of gastroduodenal ulcers. The proportion of ex-smokers was 9% before the warnings versus 7% afterwards.

The proportion of patients for whom treatment with ARCOXIA was started at 60 mg for osteoarthritis had reduced (with an increase in higher doses of 90 and 120 mg). This went from 64.66% before February 2005 to 60.09% after this date. The proportion of patients receiving 90 mg for osteoarthritis went from 25.77% to 29.8% and the proportion receiving 120 mg for osteoarthritis went from 9.58% to 10.09%.

Within the scope of the French RMP, a prospective pharmaceutical epidemiological study was requested to evaluate the characteristics of patients treated under real and correct usage conditions for ARCOXIA. This study started in January 2012 (final report expected in July 2013). It is expected to include patients spontaneously going to see a general practitioner or a rheumatologist participating in the study, and treated with either ARCOXIA or CELEBREX (426 patients per group).

In conclusion, all of this usage data shows that the 30 mg dose represents 60% of prescriptions, and that the dosages recommended by the Marketing Authorisation appear to be respected.

4.4. Status of ARCOXIA in other countries

Europe

ARCOXIA is currently refundable in 19 other countries in Europe.

Country	Reimbursement rate	Dose of ARCOXIA
Germany	100%	30, 60, 90 and 120 mg
Spain	60%	30, 60, 90 and 120 mg
Italy	100%	30, 60, 90 and 120 mg
United Kingdom	100%	30, 60, 90 and 120 mg
Belgium	75-85% (not refundable if taken concomitantly with another NSAID or a PPI)	30, 60, 90 and 120 mg
Finland	42%	30, 60, 90 and 120 mg
Greece	75%	30, 60, 90 and 120 mg
Hungary	70%	60 and 90 mg
Ireland	100%	30, 60, 90 and 120 mg
Norway	100% (with restrictions)	30, 60, 90 and 120 mg
Netherlands	100%	30, 60, 90 and 120 mg
Portugal	37%	60 and 90 mg
Slovak Republic	35-94% (depending on dose)	30, 60, 90 and 120 mg
Czech Republic	67%	30, 60, 90 and 120 mg
Romania	50%	30, 60, 90 and 120 mg
Slovenia	100%	30, 60, 90 and 120 mg
Sweden	100%	30, 60, 90 and 120 mg
Switzerland	90%	30, 60, 90 and 120 mg

On an international scale

These proprietary medicinal products received a Marketing Authorisation in 82 countries (including numerous European countries) except for the United States and Canada. Marketing Authorisation withdrawals occurred for all doses in July 2007 in Turkey and in August 2007 in Venezuela and for just the 120 mg dose in Brazil in October 2008 as the benefit/risk ratio was judged as being unfavourable.

4.5. Conclusion

Within the scope of the re-assessment of the Actual Benefit (AB) of selective COX-2 inhibitor anti-inflammatories (etoricoxib - ARCOXIA 30 and 60 mg and celecoxib - CELEBREX), no new data evaluating the efficacy of etoricoxib in the treatment of osteoarthritis has been provided by the laboratory or identified in the literature. With regard to tolerance, a meta-analysis carried out based on clinical trials (essentially the studies from the MEDAL programme for etoricoxib) and a systematic literature review on controlled observational studies was published in 2011 and confirmed, with methodological limitations being noted, that NSAIDs were associated with an increased cardiovascular risk (myocardial infarction, CVA, death from a cardiovascular cause, etc.), and in particular, etoricoxib was associated with an increase in cardiovascular related deaths.
Indeed, in the meta-analysis carried out on clinical trials[1], etoricoxib (60 and 90 mg/day) was associated with a higher risk of death from a cardiovascular cause (secondary endpoint) compared with placebo (RR = 4.07 95% CI [1.23 - 15.7]), in the same order as that for diclofenac 150 mg/day (RR = 3.98 95% CI [1.48 - 12.7]). A statistically significant increase was not found for the risk of death from a cardiovascular cause associated with celecoxib (200 to 400 mg/day): RR = 2.07, 95% CI [0.98 - 4.55]. In this meta-analysis, a statistically significant increase in the risk of CVA and myocardial infarction associated with etoricoxib and celecoxib was not found compared with placebo.
In the systematic review of the literature carried out on observational studies[2], a statistically significant increase in cardiovascular risk was observed will all 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]).

The French national pharmacovigilance follow-up and the analysis of international pharmacovigilance data covering the period from 1 April 2008 to 31 March 2011 did not highlight any new tolerance warnings for the identified risks for etoricoxib at the validated dosages in France of 30 and 60 mg for osteoarthritis.

With regard to the usage data, according to the data from the Health and retirement scheme for independent workers, from the general beneficiaries sample and the IMS DOREMA database, the 30 mg dose represented 61% of prescriptions in 2010.

Within the scope of the French Risk Management Plan, a prospective pharmaceutical epidemiological study was requested to evaluate the characteristics of patients and the correct usage of ARCOXIA, the results of which should be available in July 2013. A re-assessment of the cardiovascular risk of all NSAIDs is in the process of being carried out by the EMA.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

The Transparency Committee considers that the available data is not sufficient to amend the actual benefit of ARCOXIA:

5.1. Re-assessment of the actual benefit

Osteoarthritis is a chronic debilitating disease that can lead to a marked deterioration in the quality of life of the patient.
ARCOXIA 30 mg and 60 mg are symptomatic treatments for osteoarthritis.
ARCOXIA can be associated with, especially at high doses, arterial hypertension, oedema and congestive heart failure.

The efficacy/tolerance ratio for these medicinal products is low for osteoarthritis.

Public health benefit
Osteoarthritis is a chronic, often serious disease and a major cause of disability. It is the cause of a marked reduction in quality of life and it has a substantial psychological impact on the patient.
The financial consequences of this disease are considerable, given the level of care that is required and the loss of working days that it causes.
The public health burden of osteoarthritis is therefore considerable. The burden represented by the sub-population likely to benefit from treatment with ARCOXIA [patients that do not have contraindications, especially inadequately controlled arterial hypertension > 140-90 mmHg], is considered as substantial.

The reduction in functional limitations and incapacities brought about by osteoarthritis, as well as the improvement in the quality of life of patients with chronic diseases is a public health need that is already an established priority (Objectives 85, 87 of the Law of 9 August 2004 on public health policy, Plan to improve the quality of life of patients with chronic diseases 2007-2011).

New data does not allow the additional impact in terms of morbidity and quality of life to be confirmed for this proprietary medicinal product.
Given the absence in additional impact of ARCOXIA in terms of morbidity and quality of life compared with other NSAIDs on the one hand, and on the other, the absence of data on the conditions of use in France, this proprietary medicinal product is not of benefit to public health.

These medicinal products are second-line treatments.

There are treatment alternatives.

The actual benefit of ARCOXIA 30 mg and 60 mg remains moderate for osteoarthritis, while the conclusions are awaited from the re-assessment of the cardiovascular risk of all NSAIDs by the EMA.

5.2. Re-assessment of the Improvement in Actual Benefit

The Transparency Committee considers that the available data is not sufficient to amend the improvement in actual benefit of ARCOXIA, namely: "The proprietary medicinal products ARCOXIA 30 and 60 mg do not bring an improvement in actual benefit compared with other non-steroidal anti-inflammatories indicated for osteoarthritis."

5.3. 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 indication: "symptomatic treatment of osteoarthritis" at the dosages in the Marketing Authorisation.

5.3.1. Packaging: Appropriate for the prescription conditions.

5.3.2. Reimbursement rate: 30%