



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 April 2009

ARCOXIA 30 mg, film-coated tablet

Box of 28 (CIP: 387 980-8)

Box of 98 (CIP: 573 530-9)

ARCOXIA 60 mg, film-coated tablet

Box of 28 (CIP: 387 925-7)

Box of 50 (CIP: 573 501-9)

Applicant: MSD - CHIBRET

etoricoxib

ATC code: M01AH05

List I

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

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance (box of 28) and approved for use by hospitals (boxes of 28, 50, and 90).

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

etoricoxib, selective cyclooxygenase-2 inhibitor NSAID

1.2. Novel aspects

None. ARCOXIA is an additional NSAID from the class of selective cyclooxygenase-2 inhibitors or coxibs.

1.3. Indication

“For the symptomatic relief of osteoarthritis (OA).

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's risks.”

1.4. Dosage

“ARCOXIA is administered orally and may be taken with or without food. When rapid relief is needed, it should be noted that the medicinal product takes effect more quickly 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. Therefore: The dose for OA should not exceed 60 mg daily.”

Elderly: No dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients.

Hepatic insufficiency: in patients with mild hepatic dysfunction (Child-Pugh scores 5-6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7-9), the dose of 60 mg every other day should not be exceeded; administration of 30 mg once daily can 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 ≥ 10); therefore, its use is contra-indicated in these patients.

Renal insufficiency: No dosage adjustment is necessary for patients with creatinine clearance ≥ 30 ml/min. The use of etoricoxib in patients with creatinine clearance < 30 ml/min is contra-indicated.

Paediatric patients: etoricoxib is contra-indicated in children and adolescents under 16 years of age.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

- M : Musculo-skeletal system
- 01 : Anti-inflammatory and antirheumatic products
- A : Anti-inflammatory and antirheumatic products, non-steroids
- H : Coxibs
- 05 : etoricoxib

2.2. Medicines in the same therapeutic category

All the NSAIDs indicated for the symptomatic treatment of osteoarthritis.

2.3. Medicines with a similar therapeutic aim

All the analgesics indicated for the symptomatic treatment of osteoarthritis.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The clinical development of ARCOXIA (etoricoxib) 30 mg and 60 mg in osteoarthritis is based on seven studies which aimed to demonstrate its superiority to placebo or to the active comparator (conventional NSAIDs), or its non-inferiority to the active comparators (celecoxib or conventional NSAIDs) - see Table 1.

Table 1: Studies of the efficacy of ARCOXIA in osteoarthritis and gout

Disease	Studies	Treatment regimen	Number of patients included
Osteoarthritis of the knee and hip	018 and 019 superiority vs placebo and non-inferiority vs naproxen	etoricoxib 60 mg x1/day Placebo naproxen: 2 x 500 mg/day Initial phase of 12 weeks then 40-week extension	018 - N= 496 Pbo: 56 , Eto: 222, Nap: 218) 019 - N = 501 Pbo: 56, Eto: 224, Nap: 221
	071 and 073 superiority vs placebo and non-inferiority vs ibuprofen	Etoricoxib 30 mg/day Placebo Ibuprofen 3 x 800 mg/day 12 weeks	071: N= 528 Pbo: 104, Eto: 214, Ibu: 210 073: N = 548 Pbo: 111, Eto: 224 Nap: 213
	076 and 077 superiority vs placebo and non-inferiority vs celecoxib	Etoricoxib 30 mg/day Placebo Celecoxib 200 mg/day Initial phase of 12 weeks then 14-week extension	076- N = 599 Pbo: 127 Eto: 231 Cele: 241 077- N = 608 Pbo: 117 Eto: 244 Cele: 247
	805 non-inferiority vs diclofenac no placebo group	Etoricoxib 60 mg/day Diclofenac 150 mg/day 6 weeks	N= 516 Eto: 256 Diclo: 260

Pbo: placebo, Nap: naproxen, Eto: etoricoxib, ibu: ibuprofen, cele: celecoxib, diclo: diclofenac.

Seven controlled randomised double-blind studies (018, 019, 071, 073, 076, 077, and 805) evaluated, for 6 to 12 weeks, the efficacy and tolerance of etoricoxib (30 mg/day or 60 mg/day) in comparison with placebo or an active comparator (naproxen 1000 mg/day, ibuprofen 2400 mg/day, diclofenac 150 mg/day, or celecoxib 200 mg/day) in the treatment of osteoarthritis. In these studies, ibuprofen, naproxen, and diclofenac were used at the maximum dosages. However, in osteoarthritis, it is recommended to use the minimum effective dosage.

The populations included had similar characteristics (mean age, duration of osteoarthritis, etc.). In these studies (apart from study 805), the main aim was to demonstrate etoricoxib's superiority to placebo and, secondarily, its non-inferiority to naproxen (study 018 and 019), ibuprofen (071 and 073), or celecoxib (076 and 077). In study 805, which did not have a placebo group, the main aim was to demonstrate non-inferiority to diclofenac.

In these studies, again with the exception of study 805, the three primary efficacy endpoints were the patient's assessment of pain and functional impairment using the WOMAC* index and the patient's overall assessment of the state of the disease.

For the non-inferiority analyses, the threshold had been set at 10 mm on the VAS. The hypothesis made was that etoricoxib would be considered non-inferior to the comparator if the upper limit of the 95% confidence interval of the difference in the time weighted mean response (etoricoxib – comparator) was below the threshold of 10 mm on a 100 mm VAS for the 3 primary endpoints.

The primary analysis of the results was carried out on a modified intention-to-treat (mITT) basis, including patients who had had an initial assessment and at least one assessment after this initial assessment. A per-protocol (PP) analysis was carried out, except in the case of studies 018 and 019.

Results: Only the results of the primary analyses are described.

➤ ARCOXIA 60 mg/day versus naproxen 1 g/day - studies 018¹ and 019² (see Table 2):

Patient characteristics:

The mean age of the patients was 62 years. The mean duration of the osteoarthritis was 6.7 years. Most of the patients had gonarthrosis (78%) and 90.9% were previous users of NSAIDs.

The mITT analysis showed etoricoxib 60 mg/day and naproxen 1000 mg/day to be superior to placebo ($p < 0.001$), and etoricoxib to be non-inferior to naproxen.

The results of the PP analysis, which ought to have been carried out on account of the secondary, non-inferiority hypothesis, were requested from the company but were not supplied.

1 J Y Reginster, K Malmstrom, A Mehta et al. Evaluation of the efficacy and tolerance of etoricoxib compared with naproxen in two, 138-week randomised studies of patients with osteoarthritis. *Ann Rheum Dis* 2007;66:945–951.

2 A Leung, K. Malmstrom, A E. Gallacher et al. Efficacy and tolerability Profile of Etoricoxib in Patients with Osteoarthritis: A randomised, Double-blind, Placebo and active-comparator controlled 12-week efficacy trial. *Current medical research and opinion* 2002;18:49-58.

Table 2. Results for primary endpoints (studies 018 and 019), mITT analysis

Mean values		Placebo		Etoricoxib 60 mg/day		Naproxen 1000 mg/day		Difference in LS mean change, between the treatment groups	
		Mean baseline value	Mean value at end of study	Mean baseline value	Mean value at end of study	Mean baseline value	Mean value at end of study	Etoricoxib 60 mg/day vs. placebo	Etoricoxib 60 mg/day vs. naproxen 1000 mg/day
018	WOMAC * pain subscale	71.14	54.22	68.87	38.35	69.01	36.56	-14.67 (-20.89, -8.45) p<0.001	1.85 (-2.09, 5.79) p=NS
	WOMAC * function subscale	68.04	58.84	66.36	41.47	66.24	39.32	-16.35 (-22.47, -10.24) p<0.001	2.09 (-1.79, 5.96) p=NS
	Patient's global assessment of disease activity *	71.75	58.51	67.61	40.44	68.69	38.82	-16.60 (-23.04, -10.16) p<0.001	1.99 (-2.09, 6.07) p=NS
019	WOMAC * pain subscale	68.70	50.72	64.92	37.92	65.66	38.97	-10.44 (-16.30, -4.58) p<0.001	-0.45 (-4.17, 3.27) p=NS
	WOMAC * function subscale	68.95	52.78	64.00	41.20	63.71	41.30	-8.42 (-14.25, -2.60) p=0.005	-0.15 (-3.85, 3.54) p=NS
	Patient's global assessment of disease activity *	73.55	51.71	66.86	39.75	67.83	42.04	-9.34 (-15.53, -3.14) p=0.003	-1.75 (-5.67, 2.18) p=NS

*assessed using a visual analogue scale (VAS) running from 0 to 100 mm - LS: least squares - vs.: versus

- ARCOXIA 30 mg/day versus ibuprofen 2.4 g/ day - studies 071³ and 073⁴ (see Table 3)

Patient characteristics:

The mean age of the patients was 62 years. The mean duration of the osteoarthritis was 7.8 years in study 071 and 6.6 years in study 073. The majority of the patients had gonarthrosis (80%).

The mITT analysis (99% of the randomised population) showed etoricoxib 30 mg/day and ibuprofen to be superior to placebo, and etoricoxib to be non-inferior to ibuprofen. Similar results were obtained in the PP analysis. However, the percentage discontinuing treatment was substantial in study 073: 18.3% in the case of etoricoxib, 28% in the case of placebo, and 21.6% in the case of ibuprofen. In study 071, it was 8% with etoricoxib, 9.3% with placebo, and 12.1% with ibuprofen. The most frequent reason for these discontinuations of treatment was lack of efficacy.

3 Wiesenhutter CW et al. Evaluation of the comparative efficacy of etoricoxib and ibuprofen for treatment of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005;80:470-479.

4 Puopolo A, et al. A randomized placebo-controlled trial comparing the efficacy of etoricoxib 30 mg and ibuprofen 2400 mg for the treatment of patients with osteoarthritis. *Osteoarthritis and Cartilage* 2007; doi:10.1016/j.joca.2007.05.022

Table 3: Results for primary endpoints (studies 071 and 073), mITT analysis

Mean values			Placebo		Ibuprofen 2400 mg/day		Etoricoxib 30 mg/day		Difference in LS mean change, between the treatment groups	
			Baseline value	Value at end of study	Baseline value	Value at end of study	Baseline value	Value at end of study	Etoricoxib 30 mg/day vs. placebo (95% CI)	Etoricoxib 30 mg/day vs. ibuprofen 2400 mg/day (95% CI)
071		WOMAC * pain subscale	69.50	52.18	67.78	42.03	68.72	41.09	-10.54 (-15.47, -5.60)	-1.65 (-5.63, 2.33)
		WOMAC * function subscale	70.05	55.77	67.79	44.77	68.10	44.28	-10.14 (-14.98, -5.29)	-0.71 (-4.63, 3.20)
		Patient's global assessment of disease activity *	72.60	55.40	70.53	44.48	72.24	43.87	-11.36 (-16.57, -6.16)	-1.36 (-5.55, 2.82)
073		WOMAC * pain subscale	64.66	48.69	64.74	41.12	66.46	38.31	-11.66 (-16.31, -7.01)	-4.04 (-7.86, -0.21)
		WOMAC * function subscale	64.23	50.90	62.52	42.43	64.27	40.80	-10.15 (-14.74, -5.57)	-2.92 (-6.71, 0.87)
		Patient's global assessment of disease activity *	66.93	50.17	69.88	43.33	70.14	39.89	-11.65 (-16.81, -6.50)	-3.54 (-7.75, 0.67)

*assessed using a visual analogue scale (VAS) running from 0 to 100 mm - LS: least squares - vs.: versus

- ARCOXIA 30 mg/day versus celecoxib 200 mg/day – studies 076 and 077⁵ (see Table 4)

Patient characteristics:

The mean age was 62.4 years in study 076 and 61.8 years in study 077. The mean duration of the osteoarthritis was 8.6 years in study 076 and 7.88 years in study 077.

The mITT analysis (over 98% of the randomised population) showed etoricoxib and celecoxib to be superior to placebo, and etoricoxib to be non-inferior to celecoxib in the 2 studies. The PP analysis (82% of the mITT population in the case of study 077 and unknown in the case of study 076) showed similar results.

5 Bingham CO et al. Efficacy and tolerance of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. *Rheumatology* 2007;46:496-507

Table 4: Analysis of the time-weighted mean response in the 12-week treatment period - (mITT)

Mean values		Placebo		Etoricoxib 30 mg/day		Celecoxib 200 mg/day		Difference in LS mean change, between the treatment groups	
		Baseline value	Value at end of study	Baseline value	Value at end of study	Baseline value	Value at end of study	Etoricoxib 30 mg/day vs. placebo (95% CI)	Etoricoxib 30 mg/day vs. Celecoxib 200 mg/day (95% CI)
076	WOMAC pain subscale	66.63	54.18	67.36	39.56	67.48	42.76	-15.07 (-19.72, -10.41)	-3.12 (-7.02, 0.77)
	WOMAC function subscale	64.69	54.62	65.49	42.24	66.56	44.61	-12.86 (-17.40, -8.31)	-1.74 (-5.53, 2.05)
	Patient's global assessment of disease activity	69.10	56.71	72.18	41.32	71.25	45.04	-16.44 (-21.31, -11.57)	-4.05 (-8.11, 0.02)
077	WOMAC pain subscale	66.44	51.84	68.68	41.60	67.27	40.62	-11.56 (-16.45, -6.67)	0.14 (-3.72, 4.00)
	WOMAC function subscale	65.17	53.94	67.70	44.19	65.75	42.99	-11.46 (-16.22, -6.71)	-0.08 (-3.83, 3.67)
	Patient's global assessment of disease activity	72.30	59.38	72.98	43.84	70.11	42.56	15.86 (-20.88, -10.83)	0.06 (-3.90, 4.02)

LS: least squares - vs.: versus

➤ **ARCOXIA 60 mg/day versus diclofenac 150 mg/day - study 805⁶ (see Table 5)**

Primary endpoint: mean change in the score on the WOMAC questionnaire pain subscale after 6 weeks of treatment. The non-inferiority threshold had been set at 10 points.

The hypothesis made was that etoricoxib would be considered non-inferior to diclofenac if the upper limit of the 95% confidence interval of the mean difference in the WOMAC pain score was below the threshold of 10 points on a 100 mm VAS.

Table 5: Results for the primary endpoint of study 805 – mITT population

Mean values (studies vs. placebo)		Etoricoxib 60 mg/day		Diclofenac 50 mg x 3/day		Difference in LS mean change, between the treatment groups
		N=253		N=258		
		Baseline value	Value at end of study	Baseline value	Value at end of study	Etoricoxib 60 mg versus diclofenac 50 mg x 3 /day
805	Assessment of pain (on WOMAC pain subscale)	62.8 (17.1)	32.6 (19.2)	62.0 (17.5)	33.0 (18.9)	-0.4 (-3.2 , 2.4)
	Mean of LS of cha. vs. initial value (95% CI)	-31.3 (-33.6 , -29.0)		-30.9 (-33.2 , -28.6)		

LS: least squares - vs.: versus - cha.: change

The primary analysis of the results was carried out on an ITT basis and not on a PP basis even though this was a non-inferiority trial.

The results observed in the mITT analysis (98% of the randomised population) and PP analysis (84% of the mITT population) support non-inferiority of etoricoxib to diclofenac.

3.2. Adverse effects

The following were taken into account in the analysis of the tolerance of ARCOXIA:

- the results of the European reassessments (2002, 2004, and 2008) which concluded that etoricoxib has a favourable risk-benefit ratio,
- the relevant data from the clinical trials, including the MEDAL programme,
- the pharmacovigilance data.

6 Zacher et al. A comparison of the therapeutic efficacy and tolerability of etoricoxib and diclofenac in patients with osteoarthritis. Current Med Res and Opin 2003;19:725-736.

3.2.1. Adverse effects data from the clinical trials

The tolerance of etoricoxib (ARCOXIA) was evaluated in 7152 patients in clinical trials. The adverse effects that were most commonly encountered and attributable to etoricoxib were:

- gastrointestinal: digestive-tract disturbances (abdominal pain, flatulence, epigastric burning sensation), diarrhoea, dyspepsia, epigastric discomfort, nausea,
- cardiovascular: hypertension, peripheral oedema, lower-limb oedema, palpitations,
- neurological: dizziness, headaches,
- other: ecchymoses, asthenia, flu-like symptoms.

These principal adverse effects are described in the SPC and are similar to those of coxibs in general. Special warnings and precautions for use regarding the gastrointestinal, thrombotic cardiovascular, cardiorenal, and cutaneous effects associated with the use of etoricoxib were included in the SPC (summary of product characteristics). It is stated, among other things, that "etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses".

Gastrointestinal, cardiovascular, and renal tolerance was the subject of specific assessments, which are presented below:

➤ Cardiovascular tolerance

A combined analysis of cardiovascular tolerance in 12 studies was submitted by the company, but was not taken into account as it was only available in the form of an abstract.

Another combined analysis of renovascular-type events in 8 phase II and III studies including a total of 4770 patients was submitted⁷. The incidence of adverse events of the following kind, and discontinuations of treatment because of them, were analysed: elevated blood pressure, lower-limb oedema, increase in blood creatinine levels, and occurrence of congestive heart failure. A significant difference ($p=0.001$) between the etoricoxib 90 mg group and the placebo group was demonstrated in regard to the incidence of hypertension: 2% (30/1491) with placebo versus 3.4% (30/889) with etoricoxib 90 mg. No statistically significant difference was demonstrated in regard to the incidence of other renovascular events. Discontinuation of treatment because of renovascular adverse effects was rare.

Cardiovascular tolerance data from the MEDAL programme⁸

The primary aim of the MEDAL programme was to evaluate the non-inferiority of etoricoxib (60 mg and 90 mg combined) in comparison with diclofenac 150 mg in regard to the risk of serious thrombotic cardiovascular events on the basis of the combined results of the three studies EDGE I & II and MEDAL. These 3 studies are presented in the table 6.

7 Curtis SP, Jennifer Ng et al. Renal effects and comparator nonsteroidal anti-inflammatory drugs in controlled clinical trials. Clin. Ther, 2004, 26 :70-83.

8 Cannon et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in MEDAL program : a randomised comparison. Lancet 2006 ;368 :1771-81

Table 6: Summary and description of the 3 clinical trials that make up the MEDAL programme

	EDGE I	EDGE II	MEDAL
Primary aim	To compare the gastrointestinal tolerance of etoricoxib with that of diclofenac in osteoarthritis patients	To compare the gastrointestinal tolerance of etoricoxib with that of diclofenac in RA patients	To compare the cardiovascular events with etoricoxib and diclofenac
Numbers and disease	7111 osteoarthritis	4086 RA	23,504 patients - 17,804 (76%) osteoarthritis - 5700 (24%) RA
Treatment investigated	Etoricoxib 90 mg x 1/day vs diclofenac 50 mg x 3/day (1:1)	Etoricoxib 90 mg x 1/day vs diclofenac 75 mg x 2/day (1:1)	Etoricoxib (60 mg or 90 mg x 1/day in osteoarthritis 90 mg in RA) vs diclofenac 75 mg x 2/day (1:1) [*]
Duration of treatment [mean (max) in months]	9 (16)	19 (34) ^{**}	20.4 (12.3)

^{*}In the MEDAL study, the first 4000 osteoarthritis patients were randomised to etoricoxib 90 mg or diclofenac 75 mg x 2/day. The other osteoarthritis patients were randomised to etoricoxib 60 mg or diclofenac 75 mg x 2/day.

^{**}The duration of the EDGE II study was specified as being 2 years from the last patient randomised.

A total of 34,701 patients, 72% of whom had osteoarthritis and 28% had RA, were treated for a mean duration of 18 months (approximately 13,000 patients were treated for over 24 months).

It is strongly recommended that low-dose aspirin be prescribed to all patients at cardiovascular risk and a gastroprotective agent (PPI, misoprostol) be prescribed to all patients at gastrointestinal risk.

The primary endpoint was the incidence of confirmed arterial or venous thrombotic cardiovascular serious adverse events during treatment and up to 14 days after the last administration of the medicine.

This composite endpoint consisted of the following events: myocardial infarction (including silent MI), unstable angina, intracardiac thrombus, resuscitated cardiac arrest, thrombotic cerebrovascular accident, cerebrovascular thrombosis, transient ischaemic attack, peripheral venous thrombosis, pulmonary embolism, peripheral arterial thrombosis, and sudden and/or unexplained death.

The protocol specified that etoricoxib would be considered non-inferior to diclofenac if the upper limit of the 95% confidence interval of the relative risk of occurrence of confirmed thrombotic cardiovascular serious adverse events was below 1.3.

Results: PP and ITT analysis

Treatment was discontinued in 52.2% of the patients receiving etoricoxib and 54.4% of the patients receiving diclofenac. Discontinuation of treatment on account of clinical adverse events occurred in 19.2% of the patients treated with etoricoxib versus 19.4% of the patients treated with diclofenac.

The patients included had numerous cardiovascular and gastrointestinal risk factors (see Table 7).

Table 7: MEDAL programme: characteristics of the patients on inclusion

Demographic data	Etoricoxib (n=17,412) Etoricoxib 60 mg: n=6769; Etoricoxib 90 mg: n=10,643	Diclofenac (n=17,289) Diclofenac 50 mg x 3: n=3518 Diclofenac 75 mg x 2: n=13,771
Age (years), mean (SD)	63.2 (8.5)	63.2 (8.5)
< 65 years, n (%)	10,178 (58.5)	10,127 (58.6)
≥ 65 to < 75 years, n (%)	5201 (29.9)	5261 (30.4)
≥ 75 years, n (%)	2033 (11.7)	1901 (11.0)
Osteoarthritis, n (%)	12,533 (72.0)	12,380 (71.6)
Rheumatoid arthritis, n (%)	4878 (28.0)	4909 (28.4)
Weight (kg), mean (SD)	78.9 (18.6)	78.9 (18.5)
BMI (kg/m ²), mean (SD)	29.5 (6.1)	29.5 (6.0)
Diabetes, n (%)	1810 (10.4)	1855 (10.7)
Hypertension ² , n (%)	8109 (46.6)	8221 (47.6)
Dyslipidaemia ² , n (%)	5097 (29.3)	5034 (29.1)
Smoker, n (%)	2034 (11.7)	2037 (11.8)
Confirmed atherosclerotic CV disease [§] , n (%)	2014 (11.6)	2010 (11.6)
≥ 2 CV risk factors [¶] or confirmed atherosclerotic CV disease, n (%)	6586 (37.8)	6639 (38.4)
Use of low-dose aspirin, n (%)	6030 (34.6)	5976 (34.6)
Medicines for cardiac purposes, n (%)		
β-blocker	2806 (16.1)	2837 (16.4)
ACE inhibitor or ARB	4571 (26.3)	4535 (26.2)
Calcium inhibitor	2096 (12.0)	2149 (12.4)
Statin	2859 (16.4)	2890 (16.7)
Diuretic	3129 (18.0)	3147 (18.2)
Medicines n (%)		
Selective COX-2 NSAID	4873 (28.0)	4939 (28.6)
Non-selective NSAID	14,209 (81.6)	14,174 (82.0)
Paracetamol	10,852 (62.3)	10,765 (62.3)
High-dose aspirin	173 (1.0)	185 (1.1)
Glucocorticosteroid	2758 (15.8)	2762 (16.0)
DMARD ^{**}	2246 (12.9)	2208 (12.8)

²Clinical history at time of selection

[§]From: clinical history of myocardial infarction, angina, cerebrovascular accident, transient ischaemic attack, angioplasty, carotid artery disease, peripheral vascular disease, or aortocoronary bypass.

[¶]At least 2 of the following risk factors: history of hypertension, diabetes, dyslipidaemia, familial history of CV disease, smoking.

^{**}Disease-modifying antirheumatic drug.

No significant difference was observed between etoricoxib and diclofenac in regard to thrombotic cardiovascular adverse events (primary endpoint). In total, 643 patients in the PP population had a cardiovascular event; 320 (1.24%) were receiving etoricoxib and 323 (1.30%) were receiving diclofenac: RR = 0.95, 95% CI [0.81; 1.11]; this suggests that etoricoxib is non-inferior to diclofenac in terms of thrombotic cardiovascular risk.

Comparable results were observed in regard to arterial thrombotic events on their own and in regard to the APTC composite endpoint⁹.

However, this study has methodological limitations which make it difficult to interpret the results, namely:

- the absence of a placebo arm, given the “non-inferiority” approach,
- the absence of arguments concerning the choice of non-inferiority threshold,
- the absence of discussion of the relative disparity of the trials included, particularly in terms of their aims,
- the comparison of two doses of etoricoxib (mean - 60 mg and high dose - 90 mg) with diclofenac 150 mg (maximum authorised dose) is not relevant in that, in osteoarthritis, it is recommended that NSAIDs be used at their minimum effective dosage.

Cardiorenal effects related to the dose - SPC data

“In the MEDAL study, the incidence of congestive heart failure adverse events (discontinuations and serious events) occurred at similar rates on etoricoxib 60 mg

⁹ Antiplatelet Trialists' Collaboration, defined as the combined incidence of deaths of CV, haemorrhagic, and unknown origin, myocardial infarction, and CVA.

compared to diclofenac 150 mg but was higher for etoricoxib 90 mg compared to diclofenac 150 mg (statistically significant for 90 mg etoricoxib vs. 150 mg diclofenac in MEDAL OA cohort). The incidence of confirmed congestive heart failure adverse events (events that were serious and resulted in hospitalisation or a visit to an emergency department) was non-significantly higher with etoricoxib than diclofenac 150 mg, and this effect was dose-dependent. The incidence of discontinuations due to edema-related adverse events was higher for etoricoxib than diclofenac 150 mg, and this effect was dose-dependent (statistically significant for etoricoxib 90 mg, but not for etoricoxib 60 mg).

The cardiorenal results for EDGE and EDGE II were consistent with those described for the MEDAL Study.

In the individual MEDAL Programme studies, for etoricoxib (60 mg or 90 mg), the absolute incidence of discontinuation in any treatment group was up to 2.6% for hypertension, up to 1.9% for edema, and up to 1.1% for congestive heart failure, with higher rates of discontinuation observed with etoricoxib 90 mg than etoricoxib 60 mg.”

➤ Gastrointestinal tolerance:

A combined analysis of the tolerance data from 10 phase IIb and IV¹⁰ studies (ended in June 2003 and including 2 gastrointestinal endoscopy studies 026 and 029) carried out with etoricoxib was submitted by the company. It compared the incidence of gastrointestinal events of the PUH type (perforation, symptomatic gastroduodenal ulcers, and haemorrhage) under etoricoxib (5,10, 30, 60, 90, or 120 mg) - mean dose of 87.3 mg/day) with that under conventional NSAIDs (diclofenac 150 mg, naproxen 1000 mg, or ibuprofen 2400 mg). In total, 5441 patients were included, 3226 of whom were treated with etoricoxib and 2215 with conventional NSAIDs. The median duration of exposure to the treatment was 12.4 months in the etoricoxib group vs. 6.3 months in the conventional-NSAIDs group. The patients' mean age was 56.7 years (29% were over 65 years of age). The incidence of PUH was significantly lower with etoricoxib than with conventional NSAIDs: 1.24% vs. 2.48%, $p < 0.001$. However, the overall incidence of discontinuation due to adverse effects was similar in the two groups. The results of this combined analysis must be interpreted with caution, for the following reasons:

- because of the small number of events per dose and the heterogeneity of the doses, the diseases, and the methodology of the studies included, it is not possible to evaluate the differences between the etoricoxib doses on the basis of this analysis,
- as the numbers in the diclofenac and ibuprofen arms were very small, these results are due principally to naproxen and do not permit conclusions to be drawn for all the NSAIDs,
- no information is available on the homogeneity of the results of the studies included.

Gastrointestinal tolerance results from the MEDAL programme

No definite conclusion can be drawn from these data, firstly because the evaluation of gastrointestinal tolerance was of an exploratory nature only and secondly because a substantial percentage of patients in the 2 groups (etoricoxib and diclofenac) received PPIs. The percentage of patients taking a PPI was 39% at the start in the 2 arms, and 82% of the subjects treated with etoricoxib and with diclofenac took a PPI for a period $\geq 75\%$ of the duration of the trial¹¹. As a rough guide, the rate of confirmed upper gastrointestinal clinical events (perforation, ulcers, haemorrhage or PUH) was significantly lower with etoricoxib (1.01%) than with diclofenac (1.42%), RR = 0.69, 95% CI [0.57-0.83]. However, no difference between etoricoxib and diclofenac was shown in regard to the rate

¹⁰ Ramey DR et al. The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxib versus non-selective NSAIDs: an updated combined analysis. CMRO. 2005; 21: 715-722.

¹¹ The mean duration of the trial was 18 months.

of upper gastrointestinal events deemed to be "*complicated*"* (complicated bleeding, obstruction, and perforation): 0.45% with etoricoxib versus 0.47% with diclofenac, p=NS.

In addition, no difference between etoricoxib and diclofenac was shown in regard to the rate of confirmed lower gastrointestinal clinical events (perforation, obstruction, haemorrhage or PUH): 0.48% with etoricoxib versus 0.56% with diclofenac, RR =0.84, 95% CI [0.63-1.13]. Finally, no difference between etoricoxib and diclofenac was demonstrated in regard to upper gastrointestinal events in patients taking concomitant low-dose aspirin (approximately 33% of patients) - SPC data.

3.2.2. Pharmacovigilance data

ARCOXIA has been granted Marketing Authorisation in 70 countries. Since the first MA, which was issued in October 2001 (Mexico), there have been 13 pharmacovigilance reports, analysing a total of 3.4 million patient-years (last report - 31 March 2008). No significant signal, including from the viewpoint of possible cardiovascular adverse effects, has been demonstrated.

The marketing of ARCOXIA in France is subject to a risk management plan which includes national pharmacovigilance monitoring and a study of use in order to assess its conformity to correct practice and compliance with the Marketing Authorisation recommendations.

3.3. **Conclusion**

3.3.1 Efficacy

The efficacy of ARCOXIA (etoricoxib) 30 mg and 60 mg in osteoarthritis was assessed in 7 phase III clinical studies in which over 3700 patients were included. Etoricoxib administered at a dose of 30 or 60 mg per day brought about a significant improvement in pain, functional impairment, and the state of the disease as assessed by the patient using a visual analogue scale (100 mm VAS). The size of the effect in comparison with placebo ranged from 10.44 to 15.07 mm in the case of pain and from 8.42 to 16.35 mm in the case of functional impairment, depending on the study. In addition, non-inferiority to the active comparator: naproxen 1000 mg/day, ibuprofen 2400 mg/day, celecoxib 200 mg/day, and diclofenac 150 mg/day, defined as a difference in time-weighted mean response (etoricoxib – comparator) of less than the threshold of 10 mm on a 100 mm VAS was demonstrated.

3.3.2 Adverse effects

Gastrointestinal tolerance: upper gastrointestinal complications (perforation, ulcer, or haemorrhage), some of them fatal, were observed with etoricoxib. Although the available data suggest better gastrointestinal tolerability with etoricoxib than with non-selective NSAIDs taken at their maximum dosage and without a gastroprotective agent, it should be noted that no difference was demonstrated in respect of complicated events in the MEDAL programme. Consequently, the utmost caution is recommended in populations at risk of gastrointestinal complications (the elderly, persons with a history of ulcer or haemorrhage, persons receiving concomitant treatment with aspirin, clopidogrel, an anticoagulant, or a corticosteroid).

Cardiovascular tolerance: the available data suggest that ARCOXIA brings an increased cardiovascular risk in comparison with other NSAIDs already on the market. In the MEDAL programme, renovascular effects (hypertension, 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

* term not defined in the company's dossier

hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses.”

Cutaneous tolerance: a risk of severe skin reactions cannot be excluded with etoricoxib.

In general, the data submitted in the dossier show that ARCOXIA has efficacy comparable to that of the other NSAIDs, though poses a higher risk of hypertension.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Osteoarthritis is a chronic incapacitating disease which can lead to marked impairment of quality of life.

ARCOXIA 30 mg and 60 mg are symptomatic treatments for osteoarthritis.

Non-inferiority of ARCOXIA 30 and 60 mg to the other NSAIDs (naproxen, ibuprofen, diclofenac, celecoxib) was demonstrated in 7 clinical studies.

However, ARCOXIA can be associated with hypertension, oedema, and congestive heart failure.

The efficacy/adverse effects ratio of these proprietary products is moderate in osteoarthritis.

Public health benefit

Symptomatic osteoarthritis is a major public health burden. The public health burden represented by the subpopulation who may receive treatment with ARCOXIA [patients who do not have contraindications, in particular uncontrolled hypertension >140/90 mmHg] is regarded as considerable.

Improving the management of osteoarthritis is a public-health need that is one of the objectives of the GTNDO*. However, the therapeutic need is already met by the analgesics and NSAIDs that exist at present.

On the basis of the data from the available trials, it is not expected that this proprietary medicine will have an additional impact on morbidity/mortality and quality of life.

Consequently, it is not expected that ARCOXIA will benefit public health in this indication.

The actual benefit of ARCOXIA 30 mg and 60 mg is moderate in osteoarthritis.

4.2. Improvement in actual benefit (IAB)

The proprietary products ARCOXIA 30 and 60 mg do not provide an improvement in actual benefit in comparison with the other nonsteroidal anti-inflammatories indicated in osteoarthritis.

4.3. Therapeutic use

In symptomatic treatment of osteoarthritis, therapy should be started with paracetamol. If this fails, NSAIDs are prescribed, at low doses to begin with. They must be reserved for painful episodes and should not be prescribed on a long-term basis. Etoricoxib 30 and 60 mg, like all NSAIDs, is thus a second-line therapy.

The decision to prescribe ARCOXIA should be based on an assessment of the individual patient's risks. In particular, patients with cardiovascular risk factors (e.g. hypertension, hyperlipidaemia, diabetes, and smoking) should only be treated with etoricoxib after a careful assessment of the efficacy/adverse effects ratio. Etoricoxib is contraindicated in

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

persons with congestive heart failure, inadequately controlled hypertension, confirmed ischaemic heart disease, peripheral arterial disease, and/or a history of CVA.

Because of the possible increase in cardiovascular risks with increasing dose and duration of treatment with etoricoxib, the shortest duration possible and the lowest effective daily dose should be used.

Upper gastrointestinal complications (perforation, ulcer, or haemorrhage), some of them fatal, were observed in patients treated with etoricoxib. Caution is therefore recommended in groups who are at risk of developing a gastrointestinal complication with NSAIDs: the elderly, patients also treated with acetylsalicylic acid, an anticoagulant, or a corticosteroid by the systemic route.

4.4. Target population

According to the data in the report of the DGS/GTND¹², the prevalence of osteoarthritis is around 17% of the general population, or 9-10 million patients; only some of these osteoarthritis cases are symptomatic, however.

As a rough guide, 3 million people are reported to be affected by gonarthrosis in France¹³; however, only 1/3 of the forms are reported to be symptomatic.

Given that NSAIDs are neither a first-line nor a long-term therapy for osteoarthritis and that contraindications limit the use of etoricoxib, the target population of etoricoxib in osteoarthritis might be estimated at 1 million patients (expert opinion).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indication “symptomatic treatment of osteoarthritis” at the dosages in the Marketing Authorisation.

4.5.1 Packaging: appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 35%.

12 Groupe technique national de définition des objectifs [National technical group for the setting of public-health objectives]
13 Cooper C. Epidemiology of osteoarthritis. In: Klippel JH, Dieppe PA, eds Rheumatology, 2nd ed. London: Mosby, 1998:1–20.