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MK-0663
Etoricoxib,
Chronic Low Back Pain

PROTOCOL TITLE/NO.: A Double-Blind, Parallel-Group, 4-Week Trial to Assess the Efficacy and Safety of Etoricoxib 60 mg and Diclofenac 150 mg in Patients with Chronic Low Back Pain #806

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (62)

PUBLICATION(S):

PRIMARY THERAPY PERIOD: 29-June-2004 to 30-Mar-2005 **CLINICAL PHASE:** IV

DURATION OF TREATMENT: 4 week treatment period.

OBJECTIVE(S): The primary objectives were (1) to evaluate the efficacy of etoricoxib 60 mg for the treatment of chronic low back pain compared to diclofenac 150 mg as assessed by the Low Back Pain Intensity Scale (0- to 100-mm VAS) over four weeks of treatment and (2) to investigate the overall safety and tolerability of etoricoxib 60 mg once daily during a four week period.

The secondary objectives were (1) to compare the effects of etoricoxib 60 mg and diclofenac 150 mg treatment on chronic low back pain via responses on the Roland and Morris Disability Questionnaire (2) to compare the efficacy of etoricoxib 60 mg daily and diclofenac 150 mg daily during a four week treatment period as assessed by the Patient Global Assessment of Response to Therapy (PGART) (3) to compare the early efficacy of etoricoxib 60 mg daily and diclofenac 150 mg daily as assessed by the PGART and Low Back Pain Intensity Scale 4 hours after the first dose in the morning of days 1, 2 and 3.

STUDY DESIGN: This was a parallel-group, 4-week, double-blind study conducted under in-house blinding procedures to evaluate safety and tolerability, and to compare clinical efficacy of etoricoxib 60 mg with diclofenac 150 mg in the treatment of chronic low back pain. At the prestudy visit patients had to be routine users of either NSAIDs or paracetamol. Patients with chronic low back pain (Quebec Task Force on Spinal Disorders Class 1 or 2) with a worsening low back pain upon discontinuation of prestudy analgesic medication were studied. Eligible patients were randomized to etoricoxib 60 mg or diclofenac 150 mg for 4 weeks. Every effort was made to monitor randomization at each site to ensure that at least 80% of patients randomized into the study had used NSAIDs (traditional NSAIDs and /or COX-2 inhibitors) as prior analgesic treatment. Both treatment groups were permitted to use up to 1950 mg of paracetamol daily as rescue therapy for pain. Patients were requested to use as little study paracetamol as possible and only to treat intolerable low back pain. Clinical efficacy and safety data were collected at 1, 2 and 4 weeks of therapy. In addition, efficacy data was collected on first, second and third days of therapy 4 hours after the morning dose. Day one was considered the first day study medication was taken.

PATIENT DISPOSITION:

Overall Disposition of Patients

	Etoricoxib 60 mg	Diclofenac 150 mg	Total
SCREENED			555
RANDOMIZED	224	222	446
Male [age range†]	63 [23-81]	63 [20-78]	126 [20-81]
Female [age range†]	161 [20-85]	159 [19-81]	320 [19-85]
	N (%)	N (%)	N (%)
COMPLETED	204 (91.1)	197 (88.7)	401 (89.9)
DISCONTINUED	20 (8.9)	25 (11.3)	45 (10.1)
Clinical adverse experience	15 (6.7)	13 (5.9)	28 (6.3)
Lack of efficacy	1 (0.4)	5 (2.3)	6 (1.3)
Protocol Deviation	2 (0.9)	3 (1.4)	5 (1.1)

Lost to Follow-up	1 (0.4)	0 (0.0)	1 (0.2)
Patient was uncooperative	1 (0.4)	2 (0.9)	3 (0.7)
Patient moved	0 (0.0)	1 (0.5)	1 (0.2)
Other Reason	0 (0.0)	1 (0.5)	1 (0.2)

† Age range in years.
N (%): Number of patients (Number of patients/Number of randomized patients).

DOSAGE/FORMULATION:
Patients took daily etoricoxib 60 mg or diclofenac sodium 150 mg (three times 50 mg) in a blinded fashion in the following manner: First dose per day, one tablet of etoricoxib 60 mg, and one tablet of placebo to match diclofenac sodium 50 mg or one tablet of placebo to match etoricoxib 60 mg, and one tablet of diclofenac sodium 50 mg. Second and third dose per day, one tablet of placebo to match diclofenac sodium 50 mg or one tablet of diclofenac sodium 50 mg.

DIAGNOSIS/INCLUSION CRITERIA:
The study target population was comprised of men and women of at least 18 years old who had a low back pain that satisfies the Quebec Task Force on Spinal disorders 1 or 2. Patients had to use NSAIDs or paracetamol on a regular basis for at least 30 days prior to Visit 1 for the treatment of low back pain. At Visit 1 prior to the prestudy analgesic washout, patients had to satisfy all of the following criteria: (1) back pain equal or less than 80 mm as measured by the Low Back Pain Intensity Scale (2) patient's response to Global Assessment of Disease Status Scale had to be either "Very Well", "Well", "Fair" or "Poor". Prior to randomization and following discontinuation of all previous analgesic medication for the washout period, patients had to satisfy all of the following criteria at Visit 2: (1) back pain of at least 40 mm as assessed by the Low Back Pain Intensity Scale (2) increase of at least 10 mm on the Low Back Pain Intensity Scale as compared to Visit 1 (3) a worsening in the Patient Global Assessment of Disease Status of at least 1 point on a 5-point Likert scale as compared to Visit 1.

EVALUATION CRITERIA:
Efficacy was measured by the following questionnaires: Low Back Pain Intensity Scale (0- to 100-mm VAS) completed by patients at Day 1, 2 and 3 and at Visits 1 through 5. Roland and Morris Disability Questionnaire (0- to 24- point scale), Low Back Pain Bothersomeness Scale (0- to 4-point Likert Scale) and Patient Global Assessment of Disease Status (0- to 4-point Likert Scale) completed by patients at Visits 1 through 5. Patient's Global Assessment of Response to Therapy (PGART, 0- to 4-point Likert Scale) was completed at Day 1, 2 and 3 and Visits 3 through 5 and the Investigator's Global Assessment of Response to Therapy (IGART, 0- to 4-point Likert Scale) was completed at Visits 3 through 5.
Safety and tolerability were assessed by the incidence of adverse experiences, laboratory values and vital signs.

STATISTICAL PLANNING AND ANALYSIS:

The primary analysis was an All Patients Treated (APT) analysis of the time-weighted average response over the 4-week treatment period; response was defined as change from baseline (Flare/Randomization Visit) during the treatment period for endpoints with baseline measurements or as on-treatment values for endpoints without baseline measurements. The APT analysis included all patients who took at least one dose of study drug, had a baseline if applicable, and at least one value after the start of treatment. Efficacy variables were assessed by an Analysis of Covariance (ANCOVA) model including treatment and pre-study analgesic medication (NSAIDs, paracetamol) as terms and the baseline score of the dependent variable as covariate. The ANCOVA model was used to estimate the within-treatment group mean time-weighted average change from baseline via least squares means (LS means), the between-group difference in LS means and to construct the 95% confidence intervals (CI) for the LS means and the LS means difference. To demonstrate clinical comparability between etoricoxib 60 mg daily and diclofenac 150 mg daily for the primary endpoint, the 95% CI for the mean difference between the 2 groups in the time-weighted average response had to fall entirely within ±10 mm on a 100-mm VAS.

Safety and tolerability were assessed by clinical and/or statistical review of adverse experiences (AEs), laboratory values, and vital signs. The primary variable for the safety assessment was the incidence of clinical AEs. All patients who took study medication were included in the analysis of safety and tolerability.

RESULTS:

Efficacy:

The effect of etoricoxib 60 mg daily was comparable (equivalence range is ± 10 mm) to the effect of diclofenac 150 mg daily for the primary variable, the time weighted average change from baseline of Low Back Pain Intensity Scale (0- to 100-mm VAS) over 4 weeks of treatment (treatment difference and 95% confidence interval was 2.51 [-1.50, 6.51].

Primary Endpoint:

			Comparison between Treatments (Etoricoxib versus Diclofenac)	
Treatment Group	LSmeans	95% CI	LSmeans	95% CI
Low Back Pain Intensity TWA† change from baseline over 4 weeks of treatment				
Etoricoxib 60 mg	-32.94	[-36.25, -29.63]	2.51	[-1.50, 6.51]
Diclofenac 150 mg	-35.45	[-38.82, -32.08]	--	--
† Time Weighted Average				

Secondary Endpoints:

			Comparison between Treatments (Etoricoxib versus Diclofenac)	
Treatment Group	LSmeans	95% CI	LSmeans	95% CI
Roland and Morris Disability Questionnaire TWA† change from baseline over 4 weeks of treatment				
Etoricoxib 60 mg	-5.30	[-6.05, -4.55]	-0.23	[-1.14, 0.67]
Diclofenac 150 mg	-5.07	[-5.83, -4.31]	--	--
Patient Global Assessment of Response to Therapy TWA† over 4 weeks of treatment				
Etoricoxib 60 mg	1.76	[1.61, 1.91]	0.12	[-0.06, 0.30]
Diclofenac 150 mg	1.64	[1.49, 1.79]	--	--
Low Back Pain Intensity change from baseline at Day 1 (4 hours ± 15 minutes after morning dose)				
Etoricoxib 60 mg	-15.69	[-19.22, -12.16]	2.83	[-1.23, 6.89]
Diclofenac 150 mg	-18.52	[-21.98, -15.06]	--	--
Low Back Pain Intensity change from baseline at Day 2 (4 hours ± 15 minutes after morning dose)				

Etoricoxib 60 mg	-20.85	[-24.77, -16.93]	3.59	[-0.94, 8.13]
Diclofenac 150 mg	-24.44	[-28.35, -20.53]	--	--
Low Back Pain Intensity change from baseline at Day 3 (4 hours ± 15 minutes after morning dose)				
Etoricoxib 60 mg	-25.41	[-29.51, -21.30]	4.57	[-0.21, 9.35]
Diclofenac 150 mg	-29.98	[-34.01, -25.95]	--	--
Patient Global Assessment of Response to Therapy at Day 1 (4 hours ± 15 minutes after morning dose)				
Etoricoxib 60 mg	2.50	[2.29, 2.71]	-0.12	[-0.36, 0.12]
Diclofenac 150 mg	2.61	[2.41, 2.82]	--	--
Patient Global Assessment of Response to Therapy at Day 2 (4 hours ± 15 minutes after morning dose)				
Etoricoxib 60 mg	2.18	[1.98, 2.39]	0.09	[-0.15, 0.33]
Diclofenac 150 mg	2.10	[1.89, 2.30]	--	--
Patient Global Assessment of Response to Therapy at Day 3 (4 hours ± 15 minutes after morning dose)				
Etoricoxib 60 mg	1.92	[1.72, 2.12]	0.12	[-0.12, 0.35]
Diclofenac 150 mg	1.81	[1.61, 2.00]	--	--
† Time Weighted Average				

Safety:

Etoricoxib was generally well tolerated. There were no statistical significant differences between etoricoxib 60 mg daily and diclofenac 150 mg daily in the proportion of patients with one or more clinical AEs, drug-related AEs, serious AEs, AEs leading to discontinuation or AEs of special interest.

Adverse Experiences Summary

	Etoricoxib 60 mg N=224		Diclofenac 150 mg N=222		Difference in Percentages (Etoricoxib versus Diclofenac)	
	n	(%)	n	(%)	Estimated	95% CI
Clinical Adverse Experiences						
With one or more clinical AE	79	(35.3)	87	(39.2)	-3.9	[-12.8, 5.0]
With drug-related clinical AE†	45	(20.1)	50	(22.5)	-2.4	[-10.0, 5.2]
With serious clinical AE	3	(1.3)	2	(0.9)	0.4	[-2.0, 3.0]
With serious drug-related clinical AE†	2	(0.9)	0	(0.0)	0.9	[-0.9, 3.2]
Who died	0	(0.0)	0	(0.0)	0.0	[-1.7, 1.7]
Discontinued due to clinical AE	15	(6.7)	12	(5.4)	1.3	[-3.3, 5.9]
Adverse Events of Special Interest						
With one or more Gastrointestinal AE	30	(13.4)	44	(19.8)	-6.4	[-13.3, 0.5]
Discontinued due to Gastrointestinal AE	6	(2.7)	6	(2.7)	-0.0	[-3.4, 3.3]
With one or more Edema-related AE	6	(2.7)	6	(2.7)	-0.0	[-3.4, 3.3]
Discontinued due to Edema-related AE	4	(1.8)	1	(0.5)	1.3	[-1.0, 4.1]
With one or more Hypertension-related AE	6	(2.7)	12	(5.4)	-2.7	[-6.8, 1.1]
Discontinued due to Hypertension-related AE	0	(0.0)	0	(0.0)	0.0	[-1.7, 1.7]
With one or more liver function lab AE	2	(0.9)	7	(3.2)	-2.3	[-5.5, 0.6]
With one or more AE of congestive heart failure, pulmonary edema or cardiac failure	0	(0.0)	0	(0.0)	0.0	[-1.7, 1.7]

† Determined by the investigator to be possibly, probably or definitely drug related.

N: Number of randomized patients who took at least one dose of study drug.

CONCLUSIONS:

For patients with chronic low back pain, over 4 weeks of treatment:

- The effect of etoricoxib 60 mg daily is comparable to diclofenac 150 mg daily as assessed by Low Back Pain Intensity Scale.
- Etoricoxib is generally well tolerated over 4 weeks of treatment.

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