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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00679146
		Study Code:	KETOP_R_02693
Generic drug name:	Thiocolchicoside+Ketoprofen	Date:	07 June 2010

Title of the study:	Efficacy and safety of a fixed combination (thiocolchicoside 8 mg + ketoprofen 100 mg) compared to thiocolchicoside 8 mg administered twice a day for 7 days in patients suffering from Acute Non Specific Low Back Pain
Coordinating Investigator:	Dr Sylvie Rozenberg, Hôpital Pitié-Salpêtrière, Paris, France
Study center(s):	33 centers in Brazil, Colombia, Egypt, Guatemala, Mexico and Venezuela
Publications (reference):	Not applicable
Study period: Date first patient enrolled: 16 April 2008 Date last patient completed: 04 June 2009	Phase of development: III

Objectives:

Primary:

To demonstrate the superiority of the oral fixed dose combination (FDC) of a muscle relaxant, thiocolchicoside (TCC) to a non steroidal anti-inflammatory drug, ketoprofen, over oral TCC, on average pain within the last 24 hours in adults suffering from acute non specific low back pain with an episode of recent onset.

Secondary:

To compare the safety of the oral combination to that of oral TCC alone.

Methodology: A comparative, multicenter, randomized, double blind, double dummy, international controlled study, with two parallels groups

Number of patients: Planned: 320 | Randomized: 334 | Treated: 330

Evaluated:

	Group 1 TCC+Ketoprofen	Group 2 TCC	Total
Randomized patients	166	168	334
Safety population	164	166	330
mITT population	160	160	320
PP population	148	148	296
Sensitivity population	134	134	268

Diagnosis and criteria for inclusion:

- Age between 20 and 55 years included,
- Non specific low back pain with an acute episode of recent onset (< 48 hours) defined by average pain within the last 24 hours ≥ 50 mm on the Visual

	Analogue Scale (VAS) - Ability to understand and comply with protocol requirements - Patients who have signed and dated their written informed consent prior to initiation of the study - Low back pain of diagnosis category 1 (low back pain radiating no farther than the intergluteal fold) or 2 (low back pain radiating no farther than the knee), as defined by the International Paris Task Force on Back Pain
Investigational product: Dose: Administration:	Tablets FDC (8 mg TCC + 100 mg ketoprofen) 1 tablet of FDC (TCC 8 mg + ketoprofen 100 mg) b.i.d + 2 tablets TCC placebo b.i.d Tablets were administered orally in the morning and in the evening
Duration of treatment: 7 days	Duration of observation: 7 days and 3 visits: D0, D3 and D7.
Reference therapy: Dose: Administration:	TCC alone 2 tablets of TCC 4 mg b.i.d. + 1 tablet of FDC placebo b.i.d Tablets were administered orally in the morning and in the evening
Criteria for evaluation:	
Efficacy Safety:	Primary criterion - Average pain within the last 24 hours (VAS) at D3 Secondary criteria: - Average pain within the last 24 hours (VAS) at D7 - Pain on movement (VAS) at D0, D3 and D7 - Stiffness (Hand-to-floor distance) at D0, D3 and D7 - Disability (Roland Morris questionnaire) at D0, D3 and D7 - Patient perceived change after treatment (Global Perceived Effect) at D3 and D7 - Work Disability (Duration of sick leave, Percentage of work disability) at D0, D3 and D7 - Time to Rescue Therapy (paracetamol or acetaminophen) Solicited adverse events (AEs) at D0, D3 and D7. Vitals Signs at D0, D3 and D7.
Statistical methods:	Means, standard deviations, median and quartiles, minima and maxima were provided for continuous variables, as well as percent distributions for categorical variables. Chi-square test or Fisher's test when the expected frequency of any cell is less than 5 was used for proportions. Analysis of variance or Wilcoxon test when the statistic of Shapiro-Wilk test is lower 0.88 in one of two treatment groups was used for continuous variables. To evaluate average pain at D3 and on changes (changes from baseline to D3, from baseline to D7 and from baseline to endpoint), pain on movement, Stiffness and RDQ-24 score on changes, following models were performed : - An ANCOVA with treatment group and VAS value at baseline as covariates, - An ANCOVA on ranks with treatment group and VAS value as covariates, - A sensitivity analysis (with country as supplementary covariates). A logistic regression with treatment group and VAS value at baseline as covariates

	was performed for responder rate (average pain and pain on movement).
Summary:	
Efficacy results:	At baseline, the mean (±SD) score of average pain on VAS was not significantly different between the two treatment groups (p=0.070) with 73.7 (±13.6) mm in Group 1 and 70.8 (±15.0) mm in Group 2. At D3, the mean (±SD) VAS score of average pain decreased similarly in both groups to 37.2 (±24.4) mm in Group 1 and 35.1 (±25.8) mm in Group 2. Mean change from baseline was -36.1 (±24.3) mm, similar in both groups. At D7, the mean (±SD) VAS score of average pain was even lower in both groups: 15.4 (±19.6) mm in Group 1 and 16.0 (±21.3) mm in Group 2. There were no statistically significant differences between the two treatment groups in changes of average pain from baseline to D7 (p=0.912) as well as from baseline to Endpoint (p=0.933). Models with treatment, VAS value at baseline and country as covariates gave the same results than models with treatment and VAS value at baseline as covariates and results on PP and sensitivity population were similar to the results obtained on mITT population. The same trend was observed for secondary criteria. Overall, the mean (±SD) VAS score for pain on movement was 79.0 (±16.0) mm at baseline and decreased to 39.9 (±26.6) mm at D3 and 18.0 (±21.8) mm at D7. The reduction was similar in both groups and the difference between them was not statistically significant (p=0.889 for change from baseline to D3 and p=0.800 for change from baseline to D7). For vertical stiffness, the mean (±SD) hand to floor distance decreased from 25.8 (±16.4) cm at baseline to 10.9 (±11.0) cm at D7. A similar decrease was observed in both treatment groups. The estimate of the mean differences of change in vertical stiffness from baseline to D3, to D7 and to endpoint were not statistically significant between the two groups (p=0.903, p=0.293, p=0.800 for D3, D7 and endpoint respectively). For RDQ-24 score, the mean (±SD) RDQ-24 score was 13.8 (5.1) at baseline without statistically significant difference between the two groups (p=0.703). The mean score of RDQ-24 decreased similarly in both treatment groups at D3 and at D7. Overall, mean (±SD) RDQ-24 score was 4.0 (±4.8) at D7. Mean changes from baseline were -6.2 (±5.3) at D3 and -9.8 (±6.1) at D7. Most patients in both groups (92.2%) perceived improvement (Global Perceived Effect) from baseline to D7. Among the workers, the number of patients requiring sick leave related to back pain decreased during the study: they were 38 (24.8%) in Group 1 and 42 (27.6%) in Group 2 between baseline and D3 and they were 20 (14.2%) at D7 in both groups between D3+1 and D7. Overall, 24 patients (7.5%) had rescue therapy between D0 and D7: 10 (6.3%) in Group 1 and 14 (8.8%) in Group 2. The mean (±SD) number of days with rescue therapy was 3.3 (±1.9) in Group 2 while it was 2.0 (±1.2) in Group 1.
Safety results:	Overall, 138 patients (41.8%) experienced at least one AE: 83 (50.6%) in Group 1 and 55 (33.1%) in Group 2. Only one AE, in Group 2, was not treatment emergent. No SAEs and no deaths were reported during the study. The most frequent TEAEs were gastrointestinal disorders, particularly diarrhea

	(26.1% of the patients) and gastritis (6.7%) and they were more frequent in Group 1 (TCC+ Ketoprofen) than in Group 2 receiving TCC alone. Nausea, upper abdominal pain and abdominal pain were reported for 3.0%, 3.9% and 1.8% of the patients, respectively. Most TEAEs (68.6%) were of mild intensity and 78.2% of the TEAES were completely resolved at the end of the study. The majority of TEAEs (78.2%) were considered as possibly related to the study medication. A total of 114 patients (34.5%) experienced TEAEs possibly related to study treatment, more often in Group 1 (43.3% compared to 25.9% in Group 2). These TEAEs were essentially gastrointestinal disorders, particularly diarrhea and gastritis. These gastrointestinal disorders have already been reported in relation with ketoprofen and TCC. Thirteen (13) patients in Group 1 and nine patients in Group 2 had to permanently discontinue the study treatment because of treatment emergent adverse events. Most of these TEAEs (89.3%) were considered related to the study treatment and most of them were from the gastrointestinal disorders system organ class, particularly diarrhea. Twenty-six (26) TEAEs leading to premature discontinuation were resolved or recovering at the end of the study. Vital signs (BMI, blood pressure, heart rate) results were similar in both groups, and mean values remained stable during the course of the study.
Date of report:	03 May 2010