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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

2 SYNOPSIS

Sponsor LABORATORIOS MENARINI, S.A. C/ Alfonso XII, 587, 08918 Badalona, Barcelona (Spain) **Name of Proprietary Drug:** Enantyum® **Name of Active Ingredient:** Dexketoprofen trometamol	Individual study table referring to Part of the dossier Volume Page	(For National Authority use only)

Study title: A multicentre clinical trial to evaluate the efficacy and safety of dexketoprofen trometamol (50 mg t.i.d.) versus ketorolac (30 mg t.i.d.) and placebo by intravenous route as part of an analgesic therapy balanced with morphine, followed by oral administration, in the treatment of postoperative pain (Protocol code IC01/03/DKP; EudraCT no: 2004-001373-26).

Investigators: [redacted]

Centre(s):

Spain:

[redacted]

Argentina:

[redacted]

Publication (references): None

Study period: Date first patient included: 28/01/05 Date last patient finished: 16/10/07	**Phase:** IV

Objectives:

The primary objective was to evaluate the analgesic effect of dexketoprofen trometamol (50 mg i.v. t.i.d.) versus ketorolac (30 mg i.v. t.i.d.) and placebo, as part of an analgesic therapy balanced with morphine, in patients with postoperative pain after orthopaedic surgery, through the determination of total morphine's intake during the first 24 hours of treatment.

The secondary objectives were to evaluate: a) the analgesic effect within the first 48 hours of treatment, through the evaluation of pain intensity b) the analgesic effect within the first 48 hours of treatment, through the determination of total morphine's intake c) the analgesic effect during oral treatment phase (3 days), through the evaluation of pain intensity d) the quality of sleep during the first 48 hours of treatment e) the degree of sedation of the patient during the first 48 hours of treatment e) the safety and local tolerability of treatments f) the global treatment assessment at the end of study, or at patient's withdrawal from the study.

Methodology: Multicentre, international, randomised, double-blind, active-comparator and placebo-controlled clinical trial in parallel groups.

Number of patients (planned and analysed):

Planned: **198** patients
Randomised: **199** patients
Analysed: Safety: **198** patients
Efficacy: (1) Phase 1(intravenous): Intention to treat (ITT): **193** patients
Per protocol (PP): **160** patients
(2) Phase 2 (oral): Intention to treat oral (ITT-oral): 176 patients

The above 4 subsets for analysis were defined as follows:

- The Intention to Treat (ITT) population was defined as all randomised patients who received at least one dose of study medication and who had at least a valid assessment of the primary efficacy endpoint (administration of morphine).

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- The Intention to Treat Oral (ITT-Oral) population was defined as all ITT patients who took at least one dose of the study oral medication, had a baseline efficacy measurement and at least one corresponding post-baseline for both pain intensity variables (VAS and VRS).
- The Per Protocol (PP) population was defined as all randomized subjects who satisfied the entry criteria with no major deviation, had received all doses of the study medication (in the first 24 hours of treatment) and had valid measurements for the main outcome (self-administration of morphine through PCA pump during the first 24 hours of treatment).
- The Safety population was defined as all randomized subjects who received at least one dose of the study medication.

Diagnosis and main inclusion criteria: Male and female patients, between 18 and 75 years old, both inclusive, who underwent elective orthopaedic surgery (primary hip replacement) under spinal anaesthesia, with grade I, II or III ASA physical status and who had given their written informed consent.

Experimental drug, dose, administration route and batch no. :

Phase 1:

Dexketoprofen trometamol 50 mg/2ml ampoules (Enantyum®, Laboratorios Menarini, S.A., Spain), intravenous route (diluted up to 50 ml of physiological saline infusion, administered in 5 min). Batches no.: 0408 (exp. 01/2008), 0431 (exp. 09/2008), and 0623 (exp. 05/2010). Multiple dose (t.i.d.).

Phase 2:

Dexketoprofen trometamol 25 mg , 1 capsule containing two tablets of 12.5 mg (Enantyum®, Laboratorios Menarini, S.A., Spain), oral route. Batches no.: 04001 (exp. 01/2006), 05002 (exp. 05/2007) and 06003 (exp. 08/2008). Multiple dose (t.i.d)

Duration of therapy: Phase 1 (intravenous): Multiple dose (t.i.d.), 2 days.; Phase 2 (oral): Multiple dose (t.i.d) 3 days

Reference drugs, dose, administration route and batch no.:

Phase 1:

Ketorolac trometamol 30 mg/1ml ampoules (Toradol®, Roche Farma S.A., Spain), intravenous route (diluted up to 50 ml of physiological saline infusion, administered in 5 min), batches nº B1842 (exp. 03/2006), B1908 (exp. 02/2007) and B195301 (exp. 11/2007). Multiple dose (t.i.d.).

Placebo 2 ml ampoules, intravenous route, administered in 5 minutes), batches nº TFN0011 (exp. 11/2005), TFG0528 (exp. 06/2010), TFG0528 (exp. 06/2010).

Phase 2:

Ketorolac trometamol 10 mg (Toradol®, Roche Farma S.A., Spain), 1 capsule containing one tablet of 10 mg (Toradol® Roche Farma S.A., Spain), oral route (batches nº E4904 (exp. 03/2007), E7050 (exp. 06/2008) and E8237 (exp. 05/2009). Multiple dose (t.i.d)

Assessment Criteria

Efficacy

a) Primary variable

Evaluation of the analgesic effect by counting the amount of morphine self-administered by the patient using a PCA pump during the first 24 hours.

b) Secondary variables

Evaluation of the analgesic effect during the first 48 hours of treatment (i.v. treatment phase), through the determination of the total intake of morphine.

Evaluation of the analgesic effect during the first 48 hours of treatment (i.v. treatment phase), through the determination of pain intensity (visual analogue scale and verbal scale).

Evaluation of the quality of sleep during the first 48 hours of treatment (i.v. treatment phase) through a verbal scale.

Evaluation of the degree of sedation of the patient during the first 48 hours of treatment through a verbal scale.

Evaluation of the analgesic effect during the oral treatment phase through the determination of pain intensity (visual analogue scale and verbal scale).

The rescue medication requirements used during the oral phase of the study were accounted and used as an additional efficacy variable.

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Patient's global treatment assessment was determined by means of a 4-point verbal categorical scale at the end of the study (once both phases finalized) or at the moment of the patient's voluntary discontinuation of his/her participation in the study or at patient's withdrawal from the study.

Safety

Changes from baseline laboratory parameters and specific evaluation of bleeding parameters were assessed in the IV study phase. General and local tolerability of the drugs, by means of the spontaneous reporting by the patient, open questions to the patient at different time points and/or observation by the investigator were globally assessed both in the i.v. and the oral phase of the study.

Statistical Methods:

The variables analysed were tabulated with statistics referred to the three treatment groups (phase 1) or to the two treatment groups (phase 2), as applicable. For continuous variables mean, standard deviation (SD), minimum, percentile 25 (P25), median, percentile 75 (P75), maximum, 95%CI were calculated. For categorical variables the absolute frequency (n) and percentages (%) were calculated. Ordinal variables were described using both above tabulations. The primary variable (morphine consumption) was analysed by means of an ANOVA (analysis of variance).

The secondary pain intensity variables -VAS (mm) and VRS -c were analysed by means of an ANCOVA (covariance analysis) with the baseline value as a covariate.

For the quality of sleep and the degree of sedation variables, a non-parametric ANOVA analysis with a previous rank transformation of the original variable was performed.

Rescue medication was assessed by means of (a) a responder analysis by categorizing the response as "yes" or "no" regarding the use of rescue medication using the Fisher's exact test and (b) by assessing the amount of units of administered medication using a non-parametric ANOVA.

For the rest of items, a suitable hypothesis test was applied according to the nature of each variable: Fisher exact test for categorical variables, Student's T-Test or ANOVA for continuous variables (2 or more than two groups, respectively), and Mann-Whitney U test for ordinal scale variables or non-parametric ANOVA equivalent to Kruskal-Wallis test (for 2 or more than two groups, respectively) for non-Gaussian continuous and ordinal variables.

Regarding multiplicity adjustments for the post-hoc contrasts, a hierarchical strategy not previously foreseen was adopted. Since the alpha level was preserved, it was not necessary to perform further adjustments.

All statistical tests were applied with a 0.05 two-sided significance level.

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SUMMARY - CONCLUSIONS:
Thirty-one centres participated in the study but only twenty-one recruited patients. For the first phase a total of 199 patients were randomised and 198 receive at least one dose of intravenous treatment. One of the randomised patients was withdrawn from the study before starting treatment due to a serious adverse event while undergoing surgery (auricular fibrillation). Sixty-three patients were randomised to the DKP.TRIS group, 66 to the ketorolac group and 69 to the placebo group. One hundred and eighty four of these patients completed the intravenous phase of the study and 14 were withdrawn for different reasons.

Regarding the oral phase of the study, 184 patients started the oral treatment: 90 in the DKP.TRIS group and 94 in the ketorolac group. One hundred and sixty seven of these patients completed the oral phase and seventeen patients were withdrawn.
The main baseline characteristics are shown in the following table:

Demographic and baseline characteristics by treatment group (ITT population)

Variable		Treatment group			TOTAL
		DKP.TRIS	KETOROLAC	PLACEBO	
		(N = 61)	(N = 64)	(N = 68)	(N = 193)
Age (years)	N	61	64	68	193
	Mean (SD)	59.7 (11.0)	61.2 (12.6)	61.6 (11.2)	60.9 (11.6)
Gender					
Male	N (%)	40 (65.6%)	40 (62.5%)	42 (61.8%)	122 (63.2%)
Female	N (%)	21 (34.4%)	24 (37.5%)	26 (38.2%)	71 (36.8%)
Diagnosis					
Primary hip replacement	N (%)	58 (95.1%)	64 (100.0%)	68 (100.0%)	190 (98.4%)
Others	N (%)	3 (4.9%)	0 (0.0%)	0 (0.0%)	3 (1.6%)
Morphine titration at PARU (mg)	N	60*	63*	67*	190*
	Mean (SD)	4.4 (3.7)	4.5 (4.5)	4.7 (3.9)	4.5 (4.0)
Pain Intensity					
PARU VAS (mm)	N	61	62*	67*	190*
	Mean (SD)	34.2 (18.5)	33.90 (14.9)	37.8 (17.9)	35.4 (17.2)
Baseline VAS (mm)	N	61	64	67*	192*
	Mean (SD)	14.2 (11.5)	17.0 (9.6)	18.6 (10.6)	16.7 (10.7)
Baseline VRS					
None	N(%)	11 (18.0%)	4 (6.3%)	7(10.3%)	22 (11.4%)
Mild	N(%)	46 (75.4%)	53 (82.8%)	56 (82.4%)	155 (80.3%)
Moderate	N(%)	4 (6.6%)	6 (9.4%)	5 (7.4%)	15 (7.8%)
Severe	N(%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)

*Some patients with missing data

Source data: Appendix 16.1.9., tables 7.1.1., 7.1.3.

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EFFICACY RESULTS

Primary variable

The mean cumulative morphine consumption during the first 24 hours was 16.61±15.53 mg, 18.64±16.73 mg and 28.41±20.02 mg for DKP.TRIS, KTL and placebo, respectively ($p<0.05$ for the comparisons of both active treatments versus placebo; ANOVA).

The following table summarizes these results**:**

Morphine consumption (mg) during the first 24 h by treatment group. ITT Population

	Treatment group				
	DKP.TRIS	**KTL**	**PLACEBO**	**TOTAL**	**p-value ANOVA**
N	61	64	68	193	
mean	16.61*	18.64*	28.41	21.44	0.0003
SD	15.53	16.73	20.02	18.28	
minimum	0.00	0.00	2.00	0.00	
maximum	55.00	78.00	100.50	100.50	

*$p<0.05$ vs placebo. Source data: Appendix 16.1.9.

Secondary variables

The amount of morphine self-administered by the patient using a morphine pump (PCA) was also measured at different established time periods: 0-48h, 0-8h, 8-24h, 24-48h. Again, the results were very similar to those observed in the 24-h time-period previously exposed, with significantly lower morphine consumption in both active groups compared to placebo.

The following table summarizes these results:

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Morphine consumption by treatment group within the first 48 h of treatment. ITT Population

Variable Mean ± SD	Treatment group DKP.TRIS (N = 61)	Ketorolac (N = 64)	Placebo (N = 68)	TOTAL (N = 193)	p-value ANOVA
0-48h	25.23 ± 25.0*	26.6 ± 24.9*	42.1 ± 32.9	31.6 ± 28.9	0.0009
0-8h	8.0 ± 7.1*	8.5 ± 6.7*	14.3 ± 9.3	10.4 ± 8.3	< 0.0001
8-24h	8.6 ± 9.8*	10.1 ± 10.7*	14.1 ± 12.2	11.0 ± 11.2	0.0132
24-48h	8.6 ± 11.2*	7.9 ± 9.9*	13.7 ± 14.4	10.2 ± 12.3	0.0128

Mean ± SD; *p< 0.05 vs placebo; Source data: Appendix 16.1.9.

There were no statistically significant differences between the two active treatment groups with regard to morphine consumption at any assessed time-period.

Regarding pain intensity, although there were some differences between active treatments and placebo, the overall results indicate an adequate pain control in all treatment groups during all the treatment periods.

During the intravenous phase, the mean pain intensity scores in both VAS and verbal scales were numerically higher in the placebo group than in both active treatments until the 24 h assessment time, these differences achieving statistical significance at almost all assessment time-points ($p<0.05$; ANCOVA and Rank-ANOVA for VAS and VS analysis, respectively). In the VAS scale, the pain intensity remained below 20 mm during all the intravenous treatment phase in both active groups. This intensity score was not achieved until 24 hours in the placebo group, although the mean pain intensity was >30 mm only at T+2 and T+4. Likewise, in the VS the mean scores of pain intensity were low and remain below 1 (considered mild) in both active groups during all the intravenous treatment phase, while this value was not achieved until T+16h in the placebo group

No statistically significant differences were observed between active treatment groups (DKP.TRIS and KTL) at any time-point in any of the pain scales. The analysis of mean values of the PID gave similar outcomes compared with absolute mean pain intensity values in both pain scales.

A comparable pattern of pain intensity results (absolute values and PID) was observed during the oral treatment phase. Thus, the pain intensity assessed by VAS and VS remained below 15 mm and 1 point (considered mild), respectively, during all the oral treatment phase for both treatment groups, without statistically significant differences between them at any time.

The quality of sleep assessed during the intravenous treatment did not show statistically significant differences between treatment groups, although the percentage of patients reporting a better quality of sleep was higher for both active treatments than for placebo group at the two assessment times.

With regard to the degree of sedation, the mean scores for this variable showed a lower degree of sedation in both active treatments versus placebo, this difference achieving statistical significance for the comparison between DKP.TRIS and placebo at T+48h ($p<0.05$, Rank-ANOVA). At this time point, the percentage of patients feeling "awake" was of 96.5 %, 93.4% and 83.3%, for DKP.TRIS, KTL and placebo, respectively

Overall 23.9% of the patients needed rescue medication (Tramadol: Adolonta®) during the oral phase. The percentage of patients who took this medication was slightly lower in KTL group (19.8 %) than in DKP.TRIS group (29.2%), without statistical differences between them. Regarding the number of capsules ingested, most of the patients took only one capsule of rescue medication (39.5%).

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The overall efficacy assessment by the patients at the end of the study (that includes both intravenous and oral phases) showed no differences between groups. Most of the patients considered the efficacy of the treatment as excellent or good (more than 85% in all treatment groups); The percentage of patients considering their treatment as excellent was 58.6%, 47.5% and 35.4% in DKP.TRIS, KTL and placebo groups, respectively.

SAFETY RESULTS:

Throughout the study, 3 patients (1.5%) experienced at least 1 adverse event starting before treatment administration; 119 patients experienced at least 1 AE starting during the i.v. phase; and 87 patients started at least 1 AE onset during the oral phase. The following table (next page) shows the occurrence of adverse events and treatment-related adverse events, the occurrence of serious AEs and the treatment distribution of AEs according to intensity.

The most commonly reported AEs were classified within the Gastrointestinal system disorders, General disorders and administration site conditions. Blood and lymphatic system disorders as well as Vascular disorders were also frequently reported. This classification was similar in both i.v. and oral phases, although in i.v. phase the number of cases of nausea and vomiting was higher, probably due to the morphine consumption. It is worthy of note that the incidence of nausea and vomiting was lower in both active groups than in the placebo group. The vast majority of these events were considered as not related to study drugs and no statistically significant differences between groups were found either.

Only 5 cases were considered as serious, 2 of them occurring before starting investigational treatment. One of these 2 cases corresponded to one patient excluded from all populations (auricular fibrillation case). The other one was randomized to placebo for the i.v. phase and ketorolac for the oral phase (it corresponded to a patient suffering from pain in left hip due to bone dysplasia, leading to unscheduled hospitalization). Two SAE cases affected patients in the KTL group, and 1 in the DKP.TRIS group. None of the 5 SAEs was considered related to the study drugs. None of the 4 patients effectively treated was withdrawn from the study because of the event.

The higher incidence of clinically-relevant abnormal haematology parameters (postoperative anaemia) was observed at the end of i.v. phase, as usual after invasive surgical interventions. This was observed in all treatment groups, including placebo, with comparable mean values between DKP.TRIS and KTL.

The amount of blood in drainage was collected at T+8h, T+24h and T+48h. The mean cumulative volume collected during the first 24 h was 434 mL, 556 mL and 501 mL for placebo, DKP.TRIS and KTL groups, respectively. No statistically significant differences among treatment groups were observed. Overall, and as expected, the mean volume of blood in drainage was higher in both active groups than in the placebo group, these differences achieving statistical significance for the comparison between DKP.TRIS and placebo at T+24h and T+48h ($p<0.05$; Rank-ANOVA).

The local tolerability of intravenous administrations was good in all treatment groups. Six patients presented erythema, 4 in the placebo group, 1 in the DKP group and 1 in the KTL group). Two patients presented swelling, both of them in the placebo group.

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Occurrence of adverse events (AEs), related AEs and withdrawals (Safety population)

Variable	Treatment		
	DKP.TRIS (N = 63)	**Ketorolac** (N = 66)	**Placebo** (N = 69)
Onset pre-treatment			
No. AEs	0	2	1
No. patients with at least 1 AE	0 (0.0 %)	2 (3.0 %)	1 (1.4 %)
No. related AE	0	0	0
No. patients with at least 1 related AE.	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
No. serious AE	0	0	1
No. patients with at least 1 serious AE	0 (0.0 %)	0 (0.0 %)	1 (1.4 %)
No. serious related AE	0	0	0
Intensity of AEs			
Mild AEs	0	2	0
Moderate AEs	0	0	0
Severe AEs	0	0	1
Onset in i.v. phase			
No. AEs	72	86	116
No. patients with at least 1 AE	37 (58.7 %)	38 (57.6 %)	44 (63.8 %)
No. related AE	19	32	40
No. patients with at least 1 related AE.	12 (19.0 %)	18 (27.3 %)	20 (19.0 %)
No. serious AE	0	1	0
No. patients with at least 1 serious AE	0 (0.0 %)	1 (1.5 %)	0 (0.0 %)
No. serious related AE	0	0	0
Intensity of AEs			
Mild AEs	46	50	62
Moderate AEs	23	32	50
Severe AEs	3	4	4
Onset in oral phase	**(N = 98)**	**(N = 100)**	
No. AEs	86	83	
No. patients with at least 1 AE	49 (50.0 %)	38 (38.0 %)	
No. related AE	20	22	
No. patients with at least 1 related AE.	15 (15.3 %)	18 (18.0 %)	
No. serious AE	1	1	
No. patients with at least 1 serious AE	1 (1.0 %)	1 (1.0 %)	
No. serious related AE	0	0	
Intensity of AEs			
Mild AEs	56	57	
Moderate AEs	24	25	
Severe AEs	6	1	

N (%). Source data: Appendix 16.1.9. (tables 40.1., 40.2., 40.3., 44.2.1., 44.2.2., 44.2.3.)

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CONCLUSIONS:

The results of this study indicate that the t.i.d. i.v. administration of 50 mg DKP.TRIS during 48 hours has good analgesic efficacy both in terms of opioid-sparing effect and control of pain after hip replacement, comparable with that of ketorolac. The switching to an oral treatment during 3 further days, at the recommended doses, also suggests that DKP.TRIS provides a satisfactory control of pain comparable to that of the active control. All treatments were well tolerated and showed a good safety profile.