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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 evaluating the analgesic efficacy and safety of dexketoprofen trometamol (50 mg i.v. followed by an oral dosage of 25 mg t.i.d.) versus metamizole (2 g i.v. and 575 mg t.i.d. by oral route) for the treatment of pain subsequent to ambulatory major surgery". (Protocol code: IC01/04/DKP.TRIS). EudraCT: 2004-001789-42

Investigators [redacted]

Centre(s): Spain: [redacted]

Publication (references): None

Study period: Date first patient included: 21/02/05 Date last patient finished: 23/01/07	**Phase:** IV

Objectives: Main objective was to evaluate the analgesic effect of dexketoprofen trometamol (50 mg iv.) versus metamizole (2 g i.v.) in the immediate postoperative period (first 4 hours after intravenous route administration) in patients with pain after ambulatory major surgery. Pain intensity was assessed by using visual analogue scale (VAS) and verbal rating scales (VRS). Secondary objectives were to evaluate a) the analgesic effect of both drugs during the oral phase, using the same tools as previously described (VAS and VRS) , as well as the assessment of pain relief (PR) using VRS.; b) the need of rescue medication during both the intravenous phase and the oral phase; c) the quality of sleep during the study treatment; d) the overall efficacy at the end of treatment ; e) the safety of both treatments.

Methodology: Multicenter, randomised, double blind, and parallel active- controlled study.

Number of patients (planned and analysed):

Planned: **160** patients
Randomised: **162** patients
Analysed: Safety: 162 patients
Efficacy: Intention to treat (ITT1): 161 patients
Intention to treat (ITT2): 137 patients
Per protocol (PP): 133 patients

The above 4 subsets for analysis were defined as follows:

- The Intention to Treat 1 (ITT1) population included all randomized subjects who took at least one dose of the study treatment and underwent herniorrhaphy, had a baseline efficacy measurement and at least one corresponding post-baseline efficacy measurement for the main outcome.
- The Intention to Treat 2 (ITT2) population included all ITT1 patients who underwent intraoperative wound infiltration as required in protocol amendment #2 (see below) .
- The Per Protocol (PP) population included all randomized subjects who satisfied the entry criteria with no major deviation, had a baseline efficacy measurement and at least one corresponding post-baseline efficacy measurement for the main outcome and did not present major violations of the protocol.
- The Safety population included all randomized subjects who took at least one dose of the study medication.

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Diagnosis and main inclusion criteria: Male and female patients aged between 18 and 65 years old, who underwent ambulatory major surgery consisting of non relapsed unilateral inguinal mesh hernioplasty, with grade I or II ASA physical status and who had given their written informed consent. Patients randomized after the implementation of protocol amendment no: 2 had to undego surgical- wound infiltration with local anesthetic (mepivacain 1%),as a part of the standard intraoperative procedure.

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

Phase 1:

Dexketoprofen trometamol 50 mg/2 ml ampoules, intravenous route (15 minutes infusion), batch no.: 0418 and 0606. Single dose

Phase 2:

Dexketoprofen trometamol 25 mg (two tablets of 12.5 mg, Enantyum®, Laboratorios Menarini, S.A., Spain), oral route batch no.: 04004. and 06001. Multiple dose (t.i.d.).

Duration of therapy: Phase 1 (intravenous): Single dose; Phase 2 (oral): Multiple dose (3 days, 9 doses)

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

Metamizole 2 g/ 5ml ampoules (Nolotil®, Europharma, S.A., Spain) intravenous route (15 minutes infusion), batch number: 425490 and 525665. Single dose.

Metamizole 575 mg capsules (Nolotil®, Europharma, S.A., Spain) oral route, batch no.: 426171. and 526900. Multiple dose (t.i.d.).

Assessment Criteria

(i) Efficacy

Primary variables as defined in the protocol were the assessment of pain intensity (PI) through a visual analogue scale (VAS type Huskisson, horizontal line of 100 mm from 0=absence of pain to 100=maximium imaginable pain) and a verbal categorical scale (VRS) (from 0=no pain to 3=Severe) during the intravenous phase (first 4 hours after the administration of the first (intravenous) dose). Mean VAS value at T+4 h was selected as the main end point for analysis. Mean VRS was defined as the second main variable. This redefinition was done in order to avoid increasing type I error.

Secondary variables:

- Assessment of PI during Phase 2 (oral treatment): using the same scales as in phase 1 (VAS and VRS) just before each dose and 2 h after the first dose.
- Assessment of PR during Phase 2 (oral treatment): by a verbal categorical scale (from 0=none to 4=complete) just before each dose and 2 h after the first dose.
- Use of rescue medication and the percentage of pain-free patients at the end of treatment.
- Overall sleep quality after the first and second night, assessed by using a 4-point verbal rating scale.
- Need for rescue medication during the study period.
- Overall assessment of the efficacy by the patient, by using a 4-point verbal scale at the end of the study or when the patient was withdrawn from the study for any reason.

(ii) Safety (phase 1 and 2): (1) Assessment of adverse events (AE) through investigator observations, spontaneous reports from the patients and by an open question at different time points.

Statistical Methods:

The continuous efficacy variables were analysed by a model of ANCOVA (covariance analysis) with the baseline value as a covariate and treated using LOCF (last observation carried forward) method. This model was applied to the VAS and VRS variables assessed during the i.v. phase. For the VRS, the ANCOVA analysis was performed with a previous rank transformation of the original variable. Since the original analysis specified in the protocol was unadjusted, this initially proposed analysis was also provided for sensibility purposes. For the rest of variables, a suitable hypothesis test was applied according to the nature of each variable: Fisher exact test for categorical variables, Student's T-Test for continuous variables and Mann-Whitney U test for ordinal scale variables.

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

The main analysis was performed using the ITT1 subset. An analysis on the ITT2 and PP subsets for the primary variables was also performed to test the robustness of the results.

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SUMMARY - CONCLUSIONS:

A total of 162 patients were randomized. All of them were included in the safety analysis. Two Intention to Treat (ITT) populations were defined (ITT1 and ITT 2): Both infiltrated and non infiltrated patients (the latter non-compliant with amendment # 2) were to be allocated to ITT1 population, whereas non infiltrated patients were excluded from ITT2 population.

Only one randomized patient was excluded from the ITT1 population, (n=161). This patient, allocated to DKP.TRIS group, underwent surgical exeresis for an inguinal adenopathy, instead of the elective inguinal hernia repair. Twenty-four patients of the ITT1 population, who were non-compliant with amendment # 2, were excluded from the ITT2 population (11 patients in DKP.TRIS group and 13 patients in MTZ group). A *per protocol* analysis was performed including 133 patients who had no major protocol violation. In the main efficacy population ITT1 (161 patients) the mean age was 44.4±12.1 years (range 18-67 years). The mean weight was 74.45±10.6 kg and the mean Body Mass Index (BMI) was 25.5±3.3 kg/m^2. The majority of patients included were men (88.8%). All patients were caucasian. The intensity of pain assessed by visual analogue scale showed a mean (±SD) baseline pain of 4.01 (±10.42) mm in the DKP.TRIS group and 5.65 (±13.43) mm in the metamizole group. The baseline pain measured by verbal scale in the DKP.TRIS group was mild in 14 patients (17.1%), moderate in 3 (3.7%) and there was no pain in 65 cases (79.3%). Sixteen (20.3%) of the patients allocated to metamizole had mild pain, 3 (3.8%) moderate and 60 (66.0%) of patients declared no pain. As observed on previous data there was homogeneity within the whole demographic and clinic baseline characteristics thus making the groups comparable.

EFFICACY RESULTS:
The following results were obtained from the ITT1 population. The results obtained within ITT2 and per protocol populations (shown in the core of the report) were very consistent with the ITT1 ones herein:

Phase 1 (intravenous treatment):

Pain intensity

The main variable of the study was redefined to be the pain intensity mean scores obtained with the VAS at time 4 hours (T+4) at the end of the intravenous phase. No statistically significant differences in mean VAS scores were observed between groups at that time nor were at any other previous time (30 minutes, 1, 2 and 3 hours after infusion). The mean scores of pain intensity registered were low and always below 30 mm. Mean values of pain intensity (PI) measured by means of a verbal scale at each of the assessment times in the two treatment groups showed no statistically significant differences at time 4 hours. Those scores were low and always rated between no pain and mild pain.

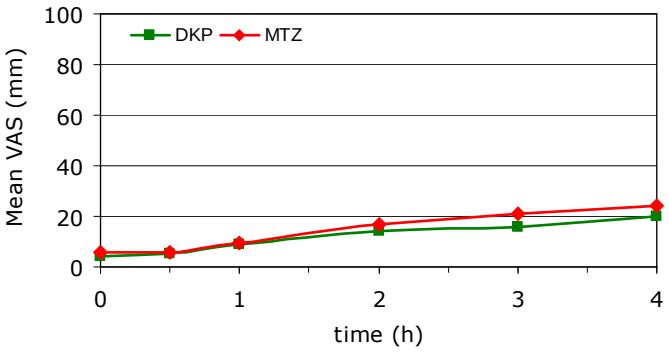

Fig. 1: Mean scores of pain intensity in the time following treatment administration. Pain intensity assessed on a visual analogue scale (from 0 to 100).

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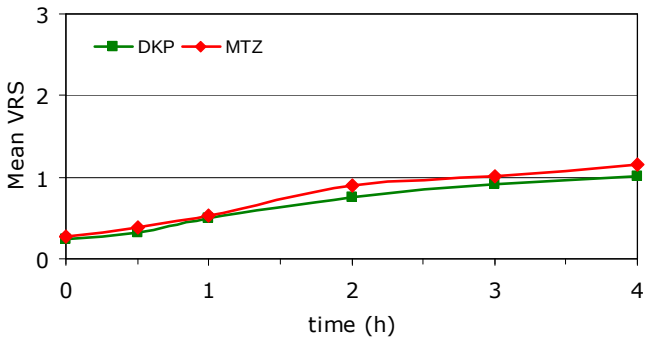

Fig. 2: Mean scores of pain intensity in the time following treatment administration. ITT1 population. Pain intensity assessed on a verbal scale (0=none to 3= severe).

Use of rescue medication

Up to the end of the intravenous phase of the study (T+4 h) , 24.39% of the patients in the DKP.TRIS group had needed rescue medication, whereas a 40.51% of the patients in the metamizole group had needed such a medication up to the same time point. This difference was statistically significant (p=0,042) in favour of the the patients who took DKP.TRIS.

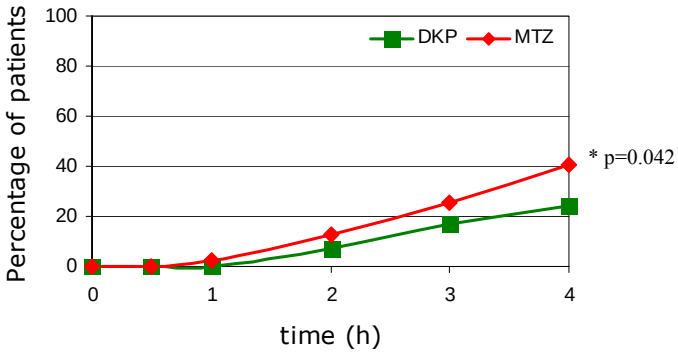

Fig. 3: Cumulative percentage of patients needing rescue medication

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Phase 2 (oral treatment):

Pain intensity

The mean scores of pain intensity when using the VAS were low and were below 30 mm. As seen in figure 4, a little increase in the pain intensity was observed at the time of taking capsule 2, ie 6-8 hours after commencing the oral phase. Afterwards, a decrease of pain intensity, as naturally occurs, was observed as time went by. No statistically significant differences were observed between groups at any time.

Results obtained by verbal scale were in consonance with the ones observed with the VAS. The patients in both groups assessed the pain intensity as mild to moderate, especially during the first day of oral therapy. Afterwards, and until the end of the study, the pain was considered mild. No statistically significant differences were observed between groups.

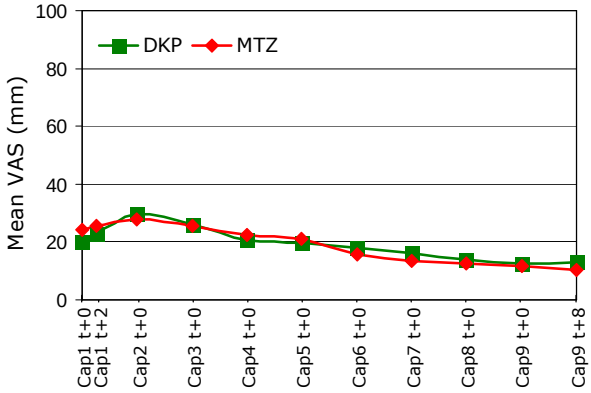

Fig. 4: Mean scores of pain intensity assessed on a visual analogue scale (from 0 to 100).

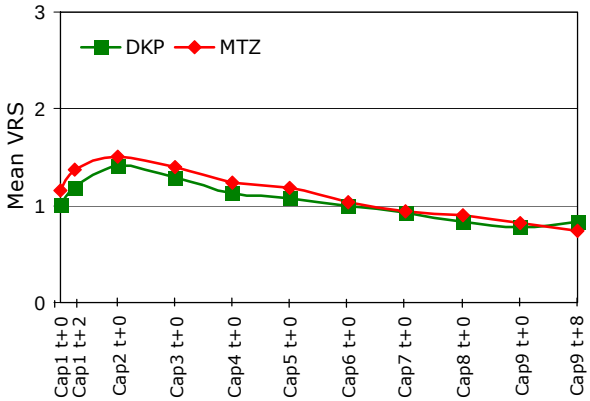

Fig 5: Mean scores of pain intensity on a verbal scale

Pain relief

Pain relief during the oral phase was assessed using a 5-point verbal rating scale from 0=none, 1=slight, 2=moderate, 3=significant and 4=total. As seen in figure 6 the assessment of pain relief done by patients was considered as moderate with a trend to be significant while time passing. This trend was observed for both treatment groups.

A statistically significant difference in favour of DKP.TRIS group was observed at 2 hours after the first oral intake medication and at the time of taking capsule number 3 (12-16 hours after first intake).

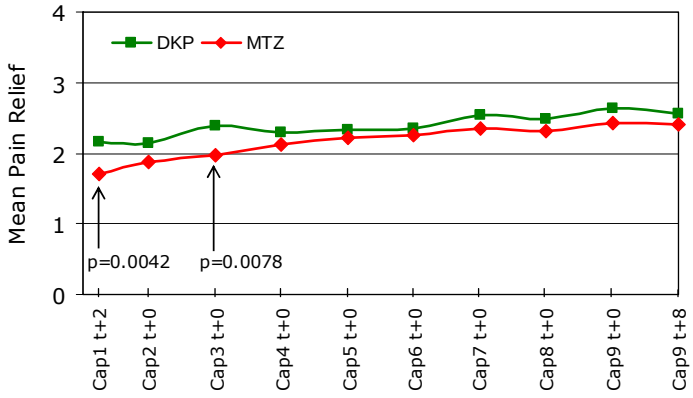

Fig. 6: Mean scores of pain relief in the time following treatment administration. Pain relief assessed on a 5-poin verbal rating scale (0=none to 4= total).

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Use of rescue medication

The need for rescue medication during the oral phase (1 g of paracetamol with a total dose not exceeding 3 g per day) is represented in figures 7 and 8. The starting point for the oral phase in figure 7 coincided with the end point for the intravenous phase (see Figure 3).
As time went by, the percentage of patients who needed rescue medication decreased. No statistically significant differences were observed between treatments either at any time or at any day of treatment.

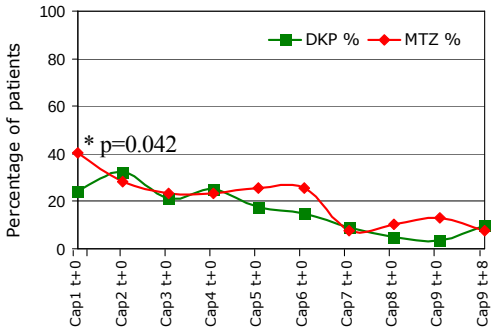

Fig. 7: Percentage of patients needing rescue medication during the oral phase.

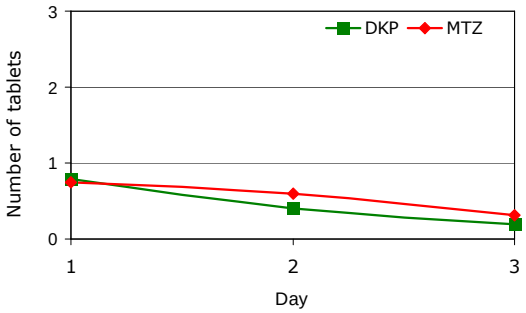

Fig 8: Number of tablets per day of rescue medication taken during the oral phase.

Quality of sleep

Quality of sleep was evaluated after first and second night. During the first night after surgery, 16.9% of patients in the DKP.TRIS group referred having slept soundly through the night, versus a 16,4% of patients who did it in the metamizole group. A 28.2% of patients in the DKP.TRIS group woke up during the night, but without pain and, thus, not requiring any medication. A 20.5% of patients in the metamizole group gave the same explanation. A 38% of patients in the DKP.TRIS group explained that they woke up during the night with mild pain, but without need for medication, versus a 42.5% of patients who did it in the MTZ group. Finally a 16.9% of patients in the DKP.TRIS group woke up during the night with pain, requiring medication. A 20.5% of patients in the MTZ group did the same. No statistically significant differences were found between groups. The results observed during the second night were very similar to the ones previously described. An overall slight trend to a better quality of sleep could be observed during the second night. Again, no statistically significant differences were observed between both groups.

Patients free from pain

As previously defined in the protocol, with a VAS score below 30 mm, the patient was considered to be free from pain. As can be observed in figure 9, that percentage was high for both treatment groups during the oral phase. It can also be observed that the lowest percentage was recorded when taking the second capsule (6-8 hours after the first oral intake). From that time point onwards, a continous increase on that percentage can be observed. At the end of the evaluation period, more than 80% of patients were free from pain. No statistically significant differences were observed between groups, except for the last assessment (cap 9 T+8h) in wich there were significant differences in favour of MTZ (p=0.0377)

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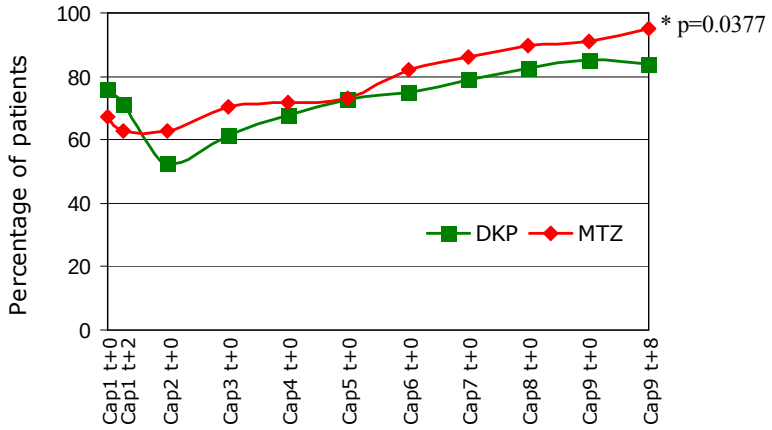

Fig. 9: Percentage of patients free from pain (VAS score under 30 mm) during the oral phase.

Treatment compliance

There were no statistically significant differences between groups with regard to patient's adherence to the treatment. From all patients who entered the oral phase (158), 71 patients (88,8%) and 74 (94,9%) patients completed the whole treatment for DKP.TRIS and MTZ respectively (safety population).

Overall efficacy assessment by patients

The overall efficacy assessment made by patients at the end of the study (including both intravenous and oral phases) showed no differences between groups. The percentage of patients considering the overall treatment efficacy as poor was less than 5% in both groups. A 58.5% of patients in the DKP.TRIS group considered the treatment efficacy as good. A 70.8% of patients in the metamizole group had the same opinion. The percentage of patients considering the overall treatment efficacy as excellent was 35.4% in the DKP.TRIS group and 26.2% in the metamizole group.

SAFETY RESULTS:

Safety population was defined as all randomised patients who had received at least one dose of the study medication. Eighty-three patients received DKP.TRIS 50 mg as a single intravenous infusion for 15 minutes. Afterwards, 80 patients received at least 1 dose of DKP.TRIS, administered by oral route at 25 mg. Seventy-nine patients received metamizole 2 g as a single intravenous infusion. Then, 78 patients received at least one dose of metamizole, which was administered by oral route at 575 mg.
Adverse events (AEs) were considered to be treatment-related if they were classified as "certain", "probable", "possible" or "unlikely related" to the study drug. Cases in which the causality was classified by the investigator as "not assessable" were also considered drug-related.
Throughout the study, 39 (24.1 %) patients showed at least 1 adverse event, 15 in the DKP.TRIS group and 24 in the metamizole group. There was a total of 52 adverse events observed, 20 (38.5%) in the DKP.TRIS group and 32 (61.5%) in the metamizole group. Table 14.4.1 shows the occurrence of adverse events and treatment-related adverse events, the occurrence of serious AEs and also the number of patients withdrawn from the study. No statistically significant differences between groups were found when comparing the number of total adverse events and the number of total related adverse events (adverse reactions).

The most frequently notified adverse events were classified as *General disorders and administration site conditions*, being pyrexia the most reported event. No statistically significant differences were found between groups. Only when assessing the *Nervous system* adverse events, statistically significant differences were found, in favour of the DKP.TRIS group. Migraine and dizziness were the most common events observed.

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Only two cases were considered as serious, both in the DKP.TRIS group. One was not related to the study drug and the other was an allergic reaction, thus, an expected one as per the drug available information.

The majority of events and reactions were of mild or moderate intensity and known and expected for the products used in the trial.

TABLE 14.4.1.

Subjects with at least one AE, related AE and serious AE. Safety Population

Variable	Treatment group		TOTAL	P-value (#)
	DKP.TRIS	MTZ		
	(N = 83) N (%)	(N = 79) N (%)	(N = 162) N (%)	
At least 1 Adverse Event				
No	68 (81.9%)	55 (69.6%)	123 (75.9%)	0.0973
Yes	15 (18.1%)	24 (30.4%)	39 (24.1%)	
TOTAL	**83 (100.0%)**	**79 (100.0%)**	**162 (100.0%)**	
At least 1 Related Adverse Event				
No	74 (89.2%)	65 (82.3%)	139 (85.8%)	0.2621
Yes	9 (10.8%)	14 (17.7%)	23 (14.2%)	
TOTAL	**83 (100.0%)**	**79 (100.0%)**	**162 (100.0%)**	
Serious Adverse Event				
No	81 (97.6%)	79 (100.0%)	160 (98.8%)	0.4972
Yes	2 (2.4%)	0 (0.0%)	2 (1.2%)	
TOTAL	**83 (100.0%)**	**79 (100.0%)**	**162 (100.0%)**	
Nº withdrawal/drop-Out due to Adverse Events	**3 (3.6%)**	**0 (0.0%)**	**3 (1.9%)**	

(#) Fisher exact test

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CONCLUSIONS:

The results of this study indicate that DKP.TRIS. 50 mg i.v. followed by an oral dosage of 25 mg t.i.d for three days (nine doses) has a good analgesic efficacy for the treatment of pain subsequent to ambulatory major surgery. This effect is comparable to that of metamizole 2 g i.v. followed by an oral dosage of 575 mg t.i.d. for three days (nine doses). However, it was observed that patients in the metamizole group took more rescue medication during the first four hours of the study (i.v. phase), the difference achieving statistical significance. With regard to the second phase of the study, the switching to oral treatment was well tolerated and showed a good analgesic profile, similar between treatments. With regard to mean scores for pain relief, a statistically significant difference in favour of DKP.TRIS group was observed 2 hours after the first oral intake medication and at the time of taking capsule number 3 (14-16 hours after first intake). The percentage of patients free from pain at the time of the last evaluation in the oral phase (cap 9 T+8h) was significantly higher for the MTZ group (p=0.0377)

With reference to safety, the majority of events were of mild or moderate intensity and known and expected for the products used in the trial. The most commonly reported adverse events were classified as *general disorders or administration site conditions*, most of them corresponding to pyrexia, although no statistically significant differences between groups were found. Notwithstanding, when comparing the *Nervous system* adverse events, a statistically significant difference in the number of events reported was found in favour of DKP.TRIS group. Migraine and dizziness were the most common reported events.

In conclusion, the analgesic efficacy of DKP.TRIS was equivalent to that of metamizole in the postoperative pain due to an ambulatory surgical intervention, with a lower need of rescue medication during the first four hours after surgery (intravenous phase) in patients receiving DKP.TRIS.

Both drugs were well tolerated and the incidence of treatment-related AEs was similar between groups. The profile of AEs was as expected for the surgery performed and the treatments studied.