ZAMBON GROUP S.P.A
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CLINICAL TRIAL REPORT SYNOPSIS

EFFICACY AND TOLERABILITY OF A TOPICAL KETOPROFEN TDS PATCH (KEOFIX®) IN THE TREATMENT OF TRAUMATIC PAINFUL SOFT-TISSUE INJURES

Protocol Code: 7148-LB-MC-02

Phase of development: III B

Product: Ketoprofen TDS patch

Indication: Traumatic painful due to soft-tissue injures

Study design: Multinational, multicentre, open label, active-control, randomised, parallel-group

Comparator drug: Diclofenac plasters

Treatment duration: 7 days

Study population: Patients with diagnosis of acute benign ankle sprain concerning external lateral ligament

Final Version, dated 03.05.2006

SYNOPSIS

Name of Sponsor/Company: Zambon Group S.p.A, Via Lillo del Duca 10, 20090 Bresso (Milan), Italy

Name of Active Ingredient: Ketoprofen TDS patch **Name of Finished Product:** Keofix®

Title of the study: Efficacy and tolerability of a topical Ketoprofen TDS patch (Keofix®) in the treatment of traumatic painful soft-tissue injures

Investigators: 23 principal investigators, located in 5 countries (Italy, Switzerland, France, Belgium and Portugal) (see appendix 16.1.4)

Study centres: 23 investigational study sites, located in 5 countries (Italy, France, Belgium, Switzerland and Portugal)

Publication (reference): None

Study period: First patient enrolled: 01/09/2004; Last patient completed: 16/08/2005

Phase of development: IIIB

Objectives: The primary objective of the present study was to compare the two study drugs in terms of change from baseline of the spontaneous pain during the previous 24 hours.

The secondary objectives of the present study were:

- To compare the two treatments in terms of change from baseline of pain intensity on active movement and functional disability restricting the daily activities;
- To compare the two treatments in terms of change from baseline of the ankle swelling;
- To compare the two study drugs in terms of change in quality of sleep, pain intensity, pain relief, and use of rescue medication (i.e. paracetamol consumption);
- To compare the two study drugs in terms of global evaluation of the therapy (assessed by the investigator), and in terms of overall judgement of the therapy and of judgment on treatment acceptability (assessed by the patient);
- To compare the two study drugs in terms of tolerability, based on the assessment and the recording of the adverse events (AEs) up to 14 days after the last patch application, on vital signs and physical examination.

Methodology:

This was a Phase IIIb, multinational, multicentre, open label, active-control, randomised, parallel-group study design, with direct individual benefit.
For each patient, the study lasted approximately 21 days. Three visits in total were scheduled. The study included the following phases and visits: inclusion visit (Visit 0); 7 days of treatment phase with 2 planned visits at Day 3-4 (Visit 1) and Day 7 ± 1 (Visit 2); follow-up by phone contact, 7 days after the application of the last medication.

Number of patients (total and in each arm):

	Randomised	ITT	PP	Safety	Completers
Total	218	216	186	218	208
Ketoprofen	109	107	91	109	102
Diclofenac	109	109	95	109	106

Diagnosis and main criteria for inclusion:

Patients were enrolled into the study if they met all the following criteria: male or female patients aged 18 to 70 years; diagnosis of acute benign ankle sprain of recent onset (within 48 hours); degree I or II in O' Donoghue classification; Stage I or IIA in Castaing classification; spontaneous pain at rest and on active movement ≥ 50 mm on the Huskisson's 100-mm VAS; non-treated ankle sprain justifying treatment with local NSAIDs; females of child-bearing age had to be surgically incapable of pregnancy, or practising an acceptable method of birth control (i.e. oral hormonal contraceptives or intrauterine device); understanding of the study and agreement to give a written informed consent; ability and agreement to comply with all study requirements; agreement to follow investigator's recommendations (e.g.: avoiding sport activities or daily activities related to ankle sprain).

Test product, dose and mode of administration, batch no: Ketoprofen TDS 100 mg patches were applied directly on the area skin overlying the painful injured region everyday (in the morning, between 7.00 and 10.00 am). Ketoprofen patches were provided in batch No. 7/05571/3, expiry date 08/2006.

Duration of treatment: 7 days (± 2 days).

Reference therapy, dose and mode of administration, batch no: Diclofenac 180 mg plasters were applied directly on the area skin overlying the painful injured region every 12 hours (in the morning, between 7.00 and 10.00 am and in the evening between 7.00 and 10.00 pm). Diclofenac plasters were provided in batch No. 031018, expiry date 10/2006.

Criteria for evaluation:

Efficacy: Primary:

- Spontaneous pain at rest during the last 24 hours measured at visit 2 (day 7 ± 1) by using a 100-mm Huskisson's VAS.

Secondary:

- Spontaneous pain at rest during the last 24 hours at any time-point using a 100-mm Huskisson's VAS.
- Functional disability restricting the daily activities during the previous 24 hours recorded by Investigators at any visit (0 = none, 1 = mild, 2 = moderate, 3 = severe);
- Ankle swelling by measuring the circumference of both ankles with a tailor tape at the malleolar level;
- Quality of sleep daily recorded by patients (0 = very bad, 1 = bad, 2 = fair, 3 = good, 4 = very good);
- Global pain intensity recorded by patients twice daily (0 = none, 'I have no pain'; 1 = mild, 'I have some pain, but it is not too bad'; 2 = moderate, 'My pain is quite marked, but does not stop me from doing anything'; 3 = severe, 'My pain is really bad and interferes with what I am doing');
- Global pain relief recorded by patients twice daily (0 = none, 'My pain has not improved at all'; 1 = a little, 'I can notice a slight improvement in my pain'; 2 = some, 'About half of my pain has gone'; 3 = a lot, 'Almost all my pain has gone'; 4 = complete, 'My pain has completely gone');
- Use of paracetamol daily recorded by patients (number of tablets per day).
- Investigator's opinion on global efficacy of treatment (0 = patient unchanged or worsened, 1 = doubtful results, 2 = patient improved, 3 = patient healed);
- Overall patient's opinion on therapy (0 = poor, 1 = fair, 2 = good, 3 = excellent);
- Patient's judgment on four separate items concerning the use and acceptability of the medication, i.e. patch/plaster application, removal, adhesion and movement ability (0 = poor, 1 = fair, 2 = good, 3 = excellent).

Safety:

- Adverse events and adverse drug reactions;
- Vital signs (heart rate, blood pressure and body weight);
- Physical examination;
- Investigator's opinion on tolerability (0 = poor, 1 = fair, 2 = good, 3 = excellent).

Statistical methods:

All randomised patients, who performed at least one visit after baseline, were analysed as efficacy population (ITT analysis). Missing data were replaced according to LOCF method. All patients included in the ITT population with protocol violations were excluded from the PP population. Tolerability was evaluated on the data set of all randomised patients that received at least one administration of study drug.

Summary statistics (mean, standard deviation, median, minimum, maximum) were provided for continuous variables; number and percentage of patients in each category were provided for categorical data.

Demographic and baseline data were compared between groups by using Chi-square test, Mann-Whitney test and Student t test for nominal, non-parametric and parametric data, respectively.

A non-inferiority test was performed on the difference between the means in the two groups of the primary variable 'Spontaneous pain at rest in the previous 24 hours' at visit 2, adjusted by the covariance analysis (ANCOVA) with

respect to the basal values. The 95% confidence interval (CI) was also calculated.

The variables 'Pain on active movement' and 'Ankle swelling' were analysed by using repeated-measures ANOVA. The variable 'Functional disability restricting the daily activities', was analysed within treatment by using the Friedman test, and between groups by using the Mann-Whitney test.

The PI and PR were analysed using the following derived variables: a) total PR, defined as the summed time-weighted PR scores up to day 3 and day 7, calculated by multiplying the PR score at each time-point by the duration (in hours) since the preceding time-point and summing these weighted values; b) SPID up to day 3 and day 7, calculated by multiplying the PID (defined as the baseline PI minus the PI at each subsequent time-point) at each time-point by the duration in hours since the preceding time-point and summing these weighted values. The comparison between groups on these variables (total PR and SPID at day 3 and day 7) was performed using the Student t test.

Quality of sleep was listed only. Paracetamol consumption was analysed between the treatment groups using Mann-Whitney Test. Parameters assessed by the Investigator's judgment (global efficacy of the treatment and global tolerability of the treatment) were analysed by the linear trend test in the comparison between groups. The overall patient's judgement on therapy was analysed by the linear trend test.

Each item of patient judgement on treatment acceptability (patch/plaster application, patch/plaster removal, movement ability, patch/plaster adhesion) was analysed by the linear trend test in the comparison between groups and by a multifactor analysis in the overall judgment.

The frequency of adverse events occurred in each treatment group was evaluated by Fisher exact test. Systolic and diastolic blood pressure and heart rate were analysed by using an analysis of (co)variance with multiple comparisons between and within treatments.

Study population:

A total number of 218 patients were recruited in the study: 109 were randomised to receive Ketoprofen and 109 were randomised to receive Diclofenac. The treatment period was successfully concluded by 208 patients, 102 in the Ketoprofen group and 106 in the Diclofenac group. Among the 10 patients who discontinued the study treatment, two of them (both in the Ketoprofene group) performed the baseline visit only (with no post-baseline follow-up) and were excluded from any efficacy analysis. A number of 7 patients in the Ketoprofen group and 3 in the Diclofenac group were prematurely withdrawn: among these, 2 (both in the Ketoprofene group) discontinued the study because healed and did not need any further treatment. Patient lost to follow-up was the leading cause of early withdrawal.

Extent of exposure and compliance:

The mean drug exposure was 7.2 ± 1.4 days (range 1-10) in the Ketoprofen group and 7.5 ± 1.2 (range 3-10) days in the Diclofenac group.

Compliance was defined as acceptable if ≥ 80% and ≤ 140% (no more than one Ketoprofen patch or two Diclofenac plasters applications missed) during the study period. The percentage of patients with compliance within the scheduled range was 95.2 in Ketoprofen group and 97.2 in Diclofenac group.

Efficacy results:

Primary efficacy variable: spontaneous pain at rest during the last 24 hours measured at visit 2

In the ITT dataset, the adjusted means were 11.3 ± 1.5 (SE) mm in the Ketoprofen group and 13.2 ± 1.5 (SE) mm in the Diclofenac group. The point estimate of the difference was -1.9 mm and the upper 95% CI of the difference between groups was 2.16 mm, thus indicating that the hypothesis of non-inferiority of Ketoprofen vs. Diclofenac (upper 95% CI of difference between adjusted means < 10 mm) was satisfied.

The adjusted means in the PP population were 11.8 ± 1.5 (SE) mm in the Ketoprofen group and 13.0 ± 1.5 (SE) mm in the Diclofenac group. The point estimate of the difference was -1.1 mm and the upper 95% CI of the difference between groups was 3.03 mm, thus confirming the non-inferiority shown in the ITT analysis.

Secondary efficacy variables:

- Spontaneous pain at rest and on activity movement in the last 24 hours, ankle swelling

No significant differences between groups were observed in the time-trend from baseline to the last visit for all the three parameters. A marked decrease from baseline was observed in both groups since the first 3-4 days of treatment for all variables.

The trends over time of spontaneous pain at rest in the last 24 hours for Ketoprofen- and Diclofenac-treated patients were very similar ($p = 0.806$ and $p = 0.723$ respectively in ITT and PP populations). Moreover, the comparison between

groups at each considered time-point resulted not statistically significant (p = 0.813 and p = 0.358, respectively for day 3-4 and day 7±1).

The same results were derived from the analyses of pain on active movement in the last 24 hours and ankle swelling (repeated-measure ANOVA: p = 0.785 and p = 0.908 for ITT and p = 0.668 and p = 0.940 in the PP dataset, respectively).

- Functional disability at daily activity during the previous 24 hours

Functional disability similarly decreased over time in the Ketoprofen- and Diclofenac-treated patients (p < 0.0001 in both groups). The rate of patients reporting moderate-to-severe functional disability decreased from 86.0% at baseline to 4.6% at the end of study among Ketoprofen-treated patients (absolute reduction: 81.4%) and from 87.2% to 6.4% among those treated with Diclofenac (absolute reduction: 80.2%). Comparisons between treatment groups were performed at any time-point and no statistically significant differences were observed.

- Investigator's opinion on global efficacy

A similar opinion was reported for the two study drugs and there were no statistically significant differences between groups (Chi square test: p = 0.498). The rates of healed patients were 65.7% in the Ketoprofen group and 58.5% in the Diclofenac group, while the rates of improved patients were 32.4% and 36.8% in the two groups, respectively.

- Patient overall judgment on therapy

The proportion of patients who gave an excellent judgment was higher among Ketoprofen-treated patients (54.8%) than in the Diclofenac group (36.8%), being the difference statistically significant (p = 0.009). There was also evidence of a linear trend in the relationship between overall judgment and treatment (p = 0.013).

- Patient judgment on treatment acceptability

Apart from the opinion on the patch/plaster removal, the patients gave a preference for Ketoprofen over Diclofenac. Ketoprofen was considered significantly better to be applied (p = 0.004), provided a better adhesion (p < 0.001) and allowed easier movement of the limb (p = 0.002) than Diclofenac.

- Patient diary evaluation: total pain relief and total pain intensity

- Total pain relief

A progressive improvement was observed in both groups. No statistically significant differences between groups in the summed time-weighted PR scores were reported at any time-point.

- Total pain intensity

A progressive improvement was observed in both groups. No statistically significant differences between groups in the SPID were reported at any time-point.

- Use of Paracetamol as rescue medication

A number of 96 patients used rescue paracetamol at least once during the study period, 44 patients in the Ketoprofen group (40.4%) and 52 in the Diclofenac group (48.6%): this difference was not statistically significant (p = 0.224). On average, the mean number of used paracetamol tablets was slightly greater among Ketoprofen-treated patients (7.2 ± 6.3 tablets) than among Diclofenac-treated patients (6.6 ± 6.2 tablets): this difference was not statistically significant (p = 0.35).

Safety results:

- Adverse events

Nine adverse events were reported by 8 patients, 4 randomized to Ketoprofen (4 events) and 4 randomized to Diclofenac (5 events). Therefore, the proportion of patients with at least one adverse event was identical in the two groups (4/109; 3.7%). All the events were non-serious and 2 events in the Ketoprofen group (blister and skin ulcer) caused early study discontinuation.

With regard to the classification by system organ class (MedDRA dictionary), the 3 events occurred among Ketoprofen-treated patients classified as "Skin & subcutaneous tissue disorders" consisted of rash macular, skin ulcer and urticaria, while the event classified as "Injury and poisoning" consisted of blister. All of them were considered as potentially treatment-related and two of them (blister and skin ulcer), with moderate intensity, led to permanent treatment discontinuation. The remaining two events in this group (urticaria and rash macular), occurring with mild intensity, did not lead to treatment discontinuation. The 2 events occurred among Diclofenac-treated patients classified as "Musculo-skeletal, connective tissue and bone disorders" consisted of neck pain and pain in limb, the 2 event classified as "Nervous system disorders" consisted of headache and muscle contraction involuntary, and the event classified among

"Gastrointestinal disorders" consisted of diarrhoea. This latter event was considered as potentially treatment-related.

- Vital signs (heart rate, blood pressure and body weight)

There was no evidence of statistically significant or clinically relevant changes in body weight, blood pressure and heart rate in either treatment group.

- Physical findings

Overall, 5 abnormal physical findings were reported for 4 patients; four abnormalities were reported at baseline for 3 and 1 patient respectively in the Ketoprofen and Diclofenac group and all of them were confirmed at the end of treatment.A new abnormal physical finding was reported at endpoint for one more patient in the Ketoprofen group (local urticaria), which was associated with an adverse event.

- Investigator's judgment of tolerability

A statistically significant difference, in favour of Ketoprofene compared to Diclofenac, was observed both in the linear trend test ($p = 0.002$) and in the rates of patients with excellent opinion ($p = 0.003$), which were 74 (70.5%) in the Ketoprofene group and 54 (50.9%) in the Diclofenac group.

Conclusions:

The main results of the present study have shown that:

- Ketoprofen patch and Diclofenac plaster administered for 7 days in the treatment of acute benign ankle sprain of the external lateral ligament provided a marked relief of primary variable 'spontaneous pain at rest during the previous 24 hours', and the effects of Ketoprofen were shown to be non-inferior than those achieved in the Diclofenac group;

- Improvements of the other signs or symptoms measured by using a VAS (i.e. pain intensity on active movement), a rating scale (i.e. functional disability restricting the daily activities) or a direct quantitative measurement (ankle swelling), as well as of daily measured total pain relief and total pain intensity, were similar in the two groups of treatment, with no significant differences between them;

- No significant differences between groups were also derived from the analysis of use of relief paracetamol and of Investigator's opinion on efficacy;

- The results of the patient's judgment on treatment acceptability showed that Ketoprofen was considered significantly better to be applied, provided a better adhesion and allowed easier movement of the limb than Diclofenac;

- Statistically significant advantages for Ketoprofen over Diclofenac were observed in the patient's opinion on therapy and in the Investigator's opinion on tolerability, mainly due to the higher rates of excellent opinion for Ketoprofen treatment compared to Diclofenac;

- The incidence of adverse events was low and identical in the two groups, and the results of safety of this study did not raise any new safety concern in the use of locally applied Ketoprofen.