Study synopsis

Name of finished product: Keofix® **Name of active ingredient:** Ketoprofen TDS patch

Title of study:

Ketoprofen TDS patch (Keofix®) in the treatment of flare-ups of non articular rheumatisms. A double-blind, double-dummy study Vs oral ketoprofen retard (200 mg capsules).

Study center(s):

Center 1
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Center 2
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Center 3
Dr. Paolo Ghiringhelli, Unità Operativa Complessa di Medicina Interna
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Center 4
Dr. Pierluigi Macchioni, U.O. di Reumatologia
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Center 6
Dr. Carlo Bancheri, Servizio di Reumatologia
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Center 7
Dr. Maurizio Muratore, Servizio di Reumatologia
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Center 8
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Center 9
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Center 10
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Center 17
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Azienda Ospedaliera di Ferrara – Arcispedale S. Anna, Ferrara

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Publication(s): None

Study period:

First patient enrolled: 08/02/2005 Last patient completed: 27/04/2006

Development phase: IIIb

Objectives:

Primary :

- To show non-inferiority of Keofix® in controlling pain on daily activity compared to Orudis Retard®.

Secondary:

- To compare the effectiveness of Keofix on spontaneous pain at rest, pain on pressure, functional impairment, pain intensity, pain relief, rescue medication consumption; global efficacy judged by patient and investigator.
- To assess local and systemic tolerability.

Methodology:

This was a multicenter, double-blind, double dummy, randomized, parallel- group study to show non- inferiority of Keofix® in controlling pain on daily activity compared to Orudis Retard®.

For each patient, the study lasted approximately 14 days:

- Inclusion visit (Visit 1)
- Fourteen days of treatment with 3 planned visits at Day 3-4 (Visit 2), Day 7 ± 1 (Visit 3) and Day 14 ± 2 (Visit 4)
- Follow-up by phone contact, 28 days after the last medication application

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Number of patients:

A total of 167 patients took part in the study, divided in 2 parallel groups:

- 84 patients were randomized in the Keofix® group
- 83 patients were randomized in the Orudis Retard® group

Indication and main criteria for inclusion:

- Male or female patients aged ≥18 years
- Diagnosis of flare-ups of non-articular rheumatisms as tendonitis, fibrositis, bursitis of recent onset (within 15 days)
- Spontaneous Pain at rest and Pain at daily activities ≥ 40 mm on the Huskisson's 100-mm VAS in the precedent 24 hrs
- Non-treated tendonitis, fibrositis, bursitis, justifying treatment with local NSAIDs
- Females of child-bearing age had to be:
    - surgically incapable of pregnancy, or
    - practicing an acceptable method of birth control (i.e. oral hormonal contraceptives or IUD),
- Understanding of the study and agreement to give a written informed consent to participate
- Ability and agreement to comply with all study requirements
- Agreement to follow investigator's recommendations (e.g.: avoid sport activities or daily activities related to tendonitis, fibrositis, bursitis)

Exclusion criteria:

- Unstable symptoms and/or rapid deterioration of PAOD during the previous 3 months
- Presence of clinically significant renal or hepatic insufficiency, or insulin-dependent type 1 diabetes
- Uncontrolled type 2 diabetes, arterial hypertension or dyslipidemia
- Any clinical condition limiting the patient’s exercise ability (angina pectoris, congestive heart failure, respiratory disease, orthopedic disease, neurological disorders)
- Active peptic ulcer disease during the previous 6 months
- Any hemorrhagic condition or history of bleeding
- Acute coronary syndrome or acute cerebrovascular episodes during the previous 6 months
- Previous revascularization procedures during the last 6 months or indication for vascular surgery
- Ischemic rest pain
- History of hypersensitivity or any form of allergic reaction, or contraindications to NSAIDs, aspirin, and NO-donating drugs
- Continuative use (> 7 days) of NSAIDs or nitrovasodilating drugs

- Current intake of phosphodiesterase type 5 inhibitors, anticoagulants, heparin, other treatments for PAOD (such as ticlopidine, clopidogrel, indobufen, defibrotide, mesoglycan, picotamide, pentoxyfylline, carnitine, sulodexide). Known or suspected alcohol, drug or medication abuse
- Life expectancy < 12 months
- Pregnancy or lactation. If woman of childbearing potential, reliable contraception should have been applied
- Participation to other investigational trials within 3 months prior to inclusion
- Previous enrolment in the present study.

Concomitant medication:

The following treatments were not allowed during the trial:

- all antalgics by any route of administration (NSAIDs, opioids etc.) except paracetamol (up to 3 g per day)
- myorelaxants (e.g. Muscoril)
- corticosteroid drugs by any route of administration
- topical medications applied to the painful region
- Any physical therapy (heat, infrared heat, short-wave or microwave diathermy, ultrasound, cold, massage, acupuncture…).

Paracetamol tablets 500 mg was supplied as rescue medication at Visit 1. Patients were instructed to take the lowest possible amount of paracetamol for pain relief and not to take more than 3g/day; in case of a higher daily intake, the patient had to contact the Investigator.

Investigational drug, doses and mode of administration:

Ketoprofen TSD/ placebo patch

Dosage form: 100 mg patch, one patch per day for 14 ± 2 days

Administration route: topical

Reference therapy:

Ketoprofen retard/ placebo (Orudis Retard®)

Dosage form: 200 mg capsules; one caps per day for 14 ± 2 days

Administration route: oral

Duration of treatment:

14 ± 2 days of treatment

Criteria for evaluation:

Efficacy Evaluation

Efficacy assessed in the CRF:

- Pain at daily activities during the last 24 hours and Spontaneous pain at rest during the previous 24 hours measured on the Huskisson's visual analogue scale (VAS);

- Pain on pressure was assessed by the investigator at visits 1, 2 (Day 3-4), 3 (Day 7 ± 1) and 4 (Day 14 ± 2) using the following 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe;
- Functional impairment restricting the daily activities during the previous 24 hrs was recorded by the investigator at visits 1, 2 (Day 3-4), 3 (Day 7 ± 1) and 4 (Day 14 ± 2) using the same 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe;

Parameters assessed in the daily diary:

- Functional impairment restricting the daily activities (using the 4-point scale): 0 = none, 1 = mild, 2 = moderate, 3 = severe;
- Pain intensity (PI)
- Pain relief (PR)

Global Evaluation of the therapy

Parameters assessed by the Investigator

- Global efficacy of the treatment was assessed at visit 4 (Day 14 ± 2) using the following 4-point scale (0 = patient unchanged or worsened, 1 = doubtful results, 2 = patient improved, 3 = patient healed);
- Global tolerability of the treatment was assessed at visit 4 (Day 14 ± 2) using the following 4-point scale (0 = poor, 1 = fair, 2 = good, 3 = excellent);

Parameters assessed by the patient

- Overall judgment of the therapy was assessed at visit 4 (Day 14 ± 2) using the following 4-point scale (0 = poor, 1 = fair, 2 = good, 3 = excellent).

Safety: the tolerability evaluation was based on the assessment and the recording of the adverse events, vital signs (blood pressure and heart rate), laboratory assessments and physical examination.

Statistical methods:

The statistical analysis was conducted by Marvin Research Srl.

Descriptive summary statistics (mean, standard deviation, minimum and maximum values for quantitative data and absolute and relative frequencies for qualitative data) were computed for all recorded variables at each planned examinations, stratified by study drug. Homogeneity of patient distribution between treatments was checked in descriptive way.

Results: The study did not demonstrate the non-inferiority of Keofix® compared to Orudis Retard® in the decrease from baseline of pain at daily activities after 14 days on treatment.

Efficacy: For the primary efficacy endpoint, values of VAS scores at visit 4 (day 14±2) are respectively 42.39±26.13 (mean ±SD) and 37.45±25.89 (mean ±SD) for the Keofix® group and for the Orudis Retard® group in the FAS population, and 38.87±24.18 (mean ±SD) and 33.09±22.42 (mean ±SD) for the Keofix® group and for the Orudis Retard® one in the PP population The point estimates of treatment difference with associated two-sided 95% Confidence Limits estimated from the ANCOVA analyses were: [+5.42, (-2.57, +13.41); p-value: 0.5482] and [+7.92, (-0.09, +15.92); p-value: 0.5873] for FAS and PP dataset respectively. Since the upper

confidence limit in both FAS and PP analyses falls beyond the pre-specified 10 mm non-inferiority threshold, the null hypothesis of inferiority of Keofix® compared to Orudis Retard® cannot be discharged.

Safety: The safety and tolerability evaluations performed showed a similar profile for both treatments groups: both treatment were well tolerated and did not cause any death or TESAE. Physical examinations performed during the follow-up showed a greater prevalence of local reactions in the Keofix® treatment group counterbalanced by a greater prevalence of systemic reactions (mainly gastrointestinal disorders) in the Orudis Retard® treatment group.

Conclusions: This study was planned to demonstrate non-inferiority of the local treatment (one patch/day) compared to the systemic treatment with the same active principle (ketoprofen) given as tablet in the retard formulation. The results of the study show a good efficacy of the patch on all symptoms and signs, while the statistical hypothesis of the non-inferiority was not rejected. It is fully understandable that the oral retard formulation could be more effective, considering the systemic effect of the active principle; on the other hand, this was paralleled by a number of systemic adverse events. The patch formulation, even if in comparison less effective, induced exclusively local adverse events, and in general was well tolerated. While it is clear that the patch administration is less effective than the systemic one, considering its efficacy and the lower risk of systemic, and potentially more dangerous, adverse events, it might be considered a valid alternative to treat mild painful conditions when systemic NSAID therapy is contraindicated**.**

Date of the report: 20/11/2006
