

# Efficacy and safety of two generic copies of nimesulide in patients with low back pain or knee osteoarthritis

## *Efficacia e sicurezza di due copie generiche di nimesulide nei pazienti che soffrono di dolore lombare o artrosi del ginocchio*

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### RIASSUNTO

*In questo studio prospettico, randomizzato, di fase IV, sono state confrontate l'efficacia e la sicurezza di due forme generiche del nimesulide, Nimulid e Tenaprost (100 mg 2 x giorno x 20 giorni), in 60 pazienti che presentavano un dolore sintomatico nella zona lombare o l'artrosi del ginocchio.*

*Entrambi i farmaci hanno ridotto in modo significativo il dolore nei pazienti con dolore lombare e artrosi del ginocchio ( $p < 0.001$ ). Rispetto al Nimulid, il Tenaprost ha mostrato effetti lievemente migliori sull'indice funzionale di Lequesne e sullo spasmo dei muscoli paravertebrali nei pazienti che presentano dolori lombari, seppur senza alcuna rilevanza clinica. Il Nimulid e il Tenaprost sono forme di nimesulide ugualmente efficaci e sicure per il trattamento del dolore della zona lombare e per l'artrosi del ginocchio. Il prezzo della dose giornaliera costituisce un parametro rilevante per la scelta del farmaco. Tuttavia, per l'autorizzazione alla registrazione dei farmaci bisognerebbe adempiere alle norme relative ai criteri di bioequivalenza.*

Reumatismo, 2009; 61(1):27-33

### INTRODUCTION

Low back pain and knee osteoarthritis are the most common causes of rheumatic troubles among all the nonspecific joint diseases. In the United States, low back pain (LBP) accounts for almost \$ 20 billion in lost productivity annually (1), and more than \$ 80 billion is spent each year in the management of the disorder (2). Currently, there is no curative treatment for both low back pain and knee osteoarthritis. Nonsteroid antiinflammatory drugs (NSAIDs) are widely used for symptomatic relief (3) due to their analgetic and anti-inflammatory effect.

Traditional NSAIDs may cause serious gastric problems including ulceration and its complications, perforation and bleeding (4). Selective COX-2 inhibitors are better tolerated drugs compared to nonselective NSAIDs and have been increasingly used for pain management in patients with osteoarthritis and low back pain over the past few years. Nimesulide, which is currently marketed in around 50 countries world-wide under different brand names, is the most widely used medication among selective COX-2 inhibitors (5). A large number of studies have confirmed that in the treatment of painful symptoms in patients with osteoarthritis of the knee and/or hip, the use of nimesulide at a daily dose of 100 mg twice daily is at least as effective as nonselective NSAIDs, such as ketoprofen (6), naproxen (7, 8), diclofenac (9). However, nimesulide has shown fewer gastrointestinal side effects than comparative drugs. The use of generic drugs has been widely advocated, mainly for economic reasons. While original drugs have to prove their efficacy and safety in a series of well-designed clinical trials, generic

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copies are not obligated to pass through such a procedure. Single dose bioequivalence studies in healthy volunteers with the original drug are all that is required to guarantee therapeutic equivalence of a generic drug prior to its marketing authorization. In the majority of cases, generic drugs perform well in clinical practice. However, when a drug has a small therapeutic index, even minimal differences in pharmacodynamics or pharmacokinetics of its generic copies could produce serious changes in efficacy and/or safety (10, 11). In a bioequivalence study conducted by Panacea Biotec Ltd., Nimulid® tablets (Panacea Biotec Ltd., New Delhi, India) were compared with Aulin® tablets (CSC Pharmaceuticals Handles GmbH, Wien, Austria). Both tablets contained 100 mg of nimesulide (12). The ratios of mean values of maximal concentration (C<sub>max</sub>) and the area under the plasma concentration versus time curve (AUC) for the two formulations were 1.17 and 1.45, respectively. The bioequivalence among two formulations of the same drug is established if the 90% CI of the ratio of mean values (i.e., AUC and C<sub>max</sub>) of the two formulations is 0.8 to 1.25 (10, 11, 13). Thus, these two formulations of nimesulide could not be considered bioequivalent. However, both formulations have been granted marketing authorization in Serbia. Incoherent or loosely implemented regulations of the marketing authorization process in countries that are in socio-economic transition could be a reason why patients and their physicians are sometimes faced with inequivalent formulations of the same drug. If a drug has a narrow therapeutic window, this may translate to significant health problems when switching from one formulation to another, and vice versa (13).

In our study, we have compared efficacy and safety of two generic formulations of selective COX-2 inhibitor nimesulide in patients with either low back pain or knee osteoarthritis. Both generic forms of nimesulide tablets, Nimulid® (Panacea Biotec Ltd., India) and Tenaprost® (Zdravlje Actavis company, previously Zdravlje Leskovac), after having been granted marketing authorization, are available with a prescription from community pharmacies.

## PATIENTS AND METHODS

A prospective, randomized double blinded phase four clinical trial was conducted at the Institute of Rheumatology of the School of Medicine, the Uni-

versity of Belgrade, from June to November 2004, in accordance with Good Clinical Practice and Declaration of Helsinki. The study was approved by the Research Ethics Committee of the Institute of Rheumatology and all the patients signed the informed consent form.

The study population consisted of two groups of 30 out-patients each (60 patients in total) with symptomatic knee osteoarthritis or low back pain. Patients were referred by their rheumatologist. To be eligible to participate in the study, patients had to be at least 18 years old and require treatment with either an analgesic or anti-inflammatory agent.

The exclusion criteria were: allergy to aspirin, the NSAIDs or a study medication, previous gastric surgery, pregnancy, lactation, active illness that could interfere with the conduct of a study (e.g., peptic ulcer disease, inflammatory bowel disease, clinically important renal or hepatic disease, based on the investigator's judgment of the patient's clinical history or on the baseline laboratory assessments) and laboratory test results outside normal reference range. Patients requiring other long-term treatment with drugs that might interfere with assessment and/or interactions with the study medication were also not eligible to participate (NSAIDs within two weeks, corticosteroids within two months, physical therapy, antidepressants, tranquilizers, and anticoagulants). Eligible patients were required to discontinue their current arthritis medication(s) for a washout period ranging from 3 to 14 days, depending on a half-life of the medication.

At the screening, the participants were randomized according to the year of birth (even or odd), independently of their diagnosis, to receive nimesulid 100 mg two times a day for 20 days as Tenaprost or Nimulid. The clinical trial pharmacist ensured that treatment codes remained confidential. During a course of the trial, the patients were not taking any other symptomatic medicamentous therapy (the NSAIDs, analgesics, corticosteroids - locally, orally and parenterally) or physical therapy. In the case when an additional analgesic was required, paracetamol (acetaminophen) tablets were also allowed. No other rescue medication was allowed during the study.

During a screening visit, data were collected from each patient on age, duration of the disease, and duration of the deterioration of a disease (a duration of an acute phase of the disease). The data regarding duration of the disease and duration of an acute phase of the disease were gathered from a

medical history and the patient's record. Objective measurements were assessed by an independent observer.

During a course of the trial, three physical check-ups were performed: at baseline, after 10 days and at the end of the treatment, i.e. 20 days after the beginning of a treatment. At each visit, pain and special parameters depending on the disease diagnosis were evaluated and adverse events were also recorded.

The intensity of pain was evaluated according to the 100 mm Visual Analogue Scale (VAS). In the patients with knee osteoarthritis, the following parameters were assessed: knee circumference (measured in centimeters across the middle of a patella), motion (flexion/extension) degree in grades and a sensitivity of tendons to palpation. In those patients with low back pain paravertebral muscle (PVM) spasm, sagittal mobility (measured by fingers-floor distance in centimeters) and the Lazarevic-Lasegue test (straight-leg raising test) were estimated. Adverse events reported by the patient or observed by the investigator during clinical evaluation were recorded. In addition, patients were questioned at each visit regarding the occurrence of adverse events using nonspecific question (i.e. Have you experienced any unusual symptoms since your last visit?).

At the end of the treatment, efficacy of the treatment was rated by the patients and by the investigators/physicians on a three point scale (1- better, 2- the same, 3- worse). The patients were asked to rate treatment: better - pain intensity was considerably lower; the same - patients experienced similar level of pain intensity; or worse - pain intensity was higher compared to state before the treatment. The physicians rated treatment: better-monitored clinical parameters were improved, the same- monitored clinical parameters remained unchanged, or worse - compared to baseline. At each visit, patients were questioned whether they were taking any paracetamol, and if that was the case, the number of paracetamol tablets was recorded.

## STATISTICAL ANALYSIS

Determination of sample size was based on a nomogram for calculating the sample size for studies using continuous variables (14), on the studies investigating efficacy of nimesulide in patients with osteoarticular pain (15, 16) and assuming an error of 0.05 and a  $\beta$  error of 0.20.

Data analyses were performed using the SPSS 16 software package for Windows (SPSS Software, Chicago, Ill).

Descriptive results for the continuous variables were reported as mean (SD) and as percentages for categorical data. Comparisons of means for continuous variables between the two treatment groups were computed with independent Student's t test, while within the same treatment group at baseline and after treatment with dependent Student's t test. Proportions for categorical data were compared with the McNamara test. The sensitivity of knee's tendons on palpation and spasm of low back paravertebral muscles between the two treatment groups were compared by the Wilcoxon test. Observed significance levels (p values) are shown for all hypothesis tests. Differences were considered statistically significant if 2-sided p-values were less than 0.05.

## RESULTS

The baseline characteristics of the patients are shown in table I. There were no significant differences between treatment groups at baseline in mean age, the mean duration of the disease and the mean duration of the acute phase of the disease (disease deterioration). Each group was composed of 86.7% women. In the group treated with Nimulid, a larger number of patients had knee osteoarthritis (60%) than low back pain; the mean duration of the disease was longer ( $7.9 \pm 7.9$  years) as well as the mean duration of the disease deterioration ( $3.6 \pm 6.8$  months) compared to the group treated with Tenaprost. However, these differences were not statistically significant. Patient's baseline pain assessment proved to be similar for both treatment groups. Indeed, no statistically significant difference was observed in the VAS scores between the two treatment groups of patients before the first drug administration.

Statistically significant time-dependent reduction in the pain level, evaluated by VAS, was found in both Tenaprost and Nimulid group (Tab. II). Statistically significant reduction in the pain level was recorded in both treatment arms after 10 as well as 20 days ( $p < 0.001$ ) of the treatment compared to baseline. After 20 days of the treatment with both Tenaprost and Nimulid, a significant decrease ( $p < 0.01$ ) in the mean value of VAS was recorded compared to the mean value of VAS after 10 days of a treatment. In the group treated with Tenaprost,

**Table I** - Baseline characteristics of patients by treatment arm (N=60).

|  | Tenaprost (n=30)   | Nimulid (n=30)     |
|--|--------------------|--------------------|
| Female (%)   | 26 (86.7%)         | 26 (86.7%)         |
| Age (years)  | 63.2±11.7 (35-83)  | 62.5±12.0 (38-84)  |
| Knee osteoarthritis (%)  | 16 (53.3%)         | 18 (60%)           |
| Low back pain  | 14 (46.7%)         | 12 (40%)           |
| Disease duration (years)   | 6.8±5.0 (0-15)     | 7.9±7.9 (0-30)     |
| Duration of disease deterioration (months)   | 3.5±3.5 (0.3-12)   | 3.6±6.8 (0-30)     |
| VAS (mm)   | 71.2±18.9 (20-100) | 67.6±18.5 (34-100) |
| Values of continuous variables are expressed as mean (SD). Categorical variables are expressed as percentages. Visual analogue pain score (VAS). |                    |                    |

the pain level decreased for 32.9% compared to baseline. In the group treated with Nimulid, the pain level reduced for 42.3% compared to baseline. There was not a statistically significant difference in achieved analgesia after 10 and 20 days between the Tenaprost and Nimulid arms.

In order to reduce pain level, paracetamol (acetaminophen) tablets were also allowed. In the Nimulid group, four of 28 people (14.3%) who completed the study used paracetamol at least once during week of treatment, for a total consumption of 8 tablets. In the Tenaprost group, two of 29 people (6.9%) used 17 tablets of paracetamol in total;

one patient used it almost every day (used 16 tablets in total), while one patient used only one tablet during the entire treatment.

Knee circumference at baseline, 10 and 20 days after the beginning of the treatment, is depicted in table II. In both treatment groups, there was not any difference in the mean knee flexion at baseline, 10 days after the beginning of the treatment, and at the end of treatment.

In addition, there was not a difference between the two treatment arms. The mean knee flexion at baseline and at the end of treatment was 105±17.5 degrees in the group treated with Tenaprost, while in

**Table II** - Patient's characteristics by treatment arm at baseline, 10, and 20 days after the beginning of treatment (N=60).

|  | Tenaprost (n=30)                  |                                   |                                  | Nimulid (n=30)                    |                                   |                                   |
|--|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
|  | Baseline                          | 10 days after                     | 20 days after                    | Baseline                          | 10 days after                     | 20 days after                     |
| VAS (mm)<br>(N=60)   | 71.2±18.9<br>(20-100)             | 54.1±21.3<br>(20-100)**           | 47.8±25.2<br>(0-100)**<br>(n=29) | 67.6±18.5<br>(34-100)<br>(n=30)   | 48.3±21.5<br>(5-90)**<br>(n=29)†  | 39.0±20.0<br>(5-80)**<br>(n=28)†† |
| Knee circumference<br>(N=34)   | 42.1±4.6<br>(35.0-52.5)<br>(n=16) | 41.8±4.6<br>(35.0-52.5)<br>(n=16) | 41.6±4.8<br>(33.5-52)<br>(n=16)  | 40.2±4.4<br>(34.0-47.0)<br>(n=18) | 40.3±4.1<br>(34.0-47.0)<br>(n=17) | 40.0±3.9<br>(34.0-46.0)<br>(n=17) |
| KTS<br>(N=34)  | 14 (87.5%)<br>(n=16)              | 11 (68.8%)<br>(n=16)              | 9 (56.3%)*<br>(n=16)             | 17 (94.4%)†<br>(n=18)             | 16 (94.2%)<br>(n=17)              | 8 (47.1%)*<br>(n=17)              |
| LT<br>(N=26)   | 65.7±21.7<br>(0-90)<br>(n=14)     | 68.6±22.1<br>(0-90)<br>(n=14)     | 80.8±13.2*<br>(n=13)             | 75.4±11.6<br>(50-90)<br>(n=12)    | 78.8±11.7<br>(60-90)<br>(n=12)    | 81.8±12.5<br>(n=11)               |
| FFD (cm)<br>(N=26)   | 29±13.4<br>(10-50)<br>(n=14)      | 24.2±15.3<br>(0-40)<br>(n=14)     | 20.7±17.9<br>(0-50)*<br>(n=14)   | 35±16.4<br>(12-80)<br>(n=12)      | 27.2±14.2<br>(0-50)<br>(n=12)     | 23.5±18.9<br>(0-50)*<br>(n=12)    |
| PVM Spasm<br>(N=26)  | 12 (85.7%)<br>(n=14)              | 8 (57.1%)<br>(n=14)               | 5 (35.7%)*<br>(n=13)†            | 8 (66.7%)<br>(n=12)               | 7 (58.3%)<br>(n=12)               | 5 (45.5%)<br>(n=11)†              |
| Visual analogue pain score (VAS). The knee's tendons sensitivity on palpation (KTS). LT- the Lazarevic-Laseguc test. Fingers-floor distance (FFD). Paravertebral muscles (PVM). n=30 per treatment group, if it is not otherwise indicated. Valid percentages are given, i.e. missing data are not included. Variables are expressed as mean (SD). *p<0.05; **p<0.01. †One patient was lost to follow up. ††Two patients were lost to follow up. |                                   |                                   |                                  |                                   |                                   |                                   |

the group treated with Nimulid, it was  $130 \pm 18.2$  degrees (data not shown).

In the group randomized to Nimulid, a higher percentage of patients (94.4%) had knee tendons sensitive to palpation compared to the group randomized to Tenaprost (87.5%). However, this difference was not statistically significant (Tab. II). After 10 days of the treatment with Tenaprost, sensitivity of knee tendons to palpation was recorded in fewer patients compared to baseline (68.8 vs. 87.5%), but this difference was also not statistically significant. In the group treated with Nimulid after 10 days of treatment, the difference in the percentage of patients with knee tendons sensitive to palpation was almost negligible compared to baseline (94.2% vs. 94.4%). However, 20 days of treatment in both treatment groups showed that the percentage of patients who had knee tendons sensitive to palpation was statistically significantly lower compared to baseline ( $p < 0.05$ ). There was not a difference in the percentage of patients with knee tendons sensitive on palpation between the two treatment arms.

In table II, the Lasegue test for patients suffering from low back pain by treatment group is depicted. Although 10 days of treatment in both groups showed that the Lasegue test increased compared to baseline, the difference was not statistically significant in any of the treatment groups. The Lasegue test was statistically significantly higher after 20 days of treatment with both Tenaprost and Nimulid ( $p < 0.05$ ) compared to baseline. The statistically significant difference was not found in the Lasegue test between the two treatment groups at baseline, 10 and 20 days after the beginning of the treatment.

Table II shows sagittal spine mobility in the two treatment groups. Ten days after the beginning of the treatment, sagittal spine mobility improved in both treatment groups compared to baseline, but this difference was not statistically significant. On

the other hand, after 20 days of treatment, a statistically significant difference was observed in sagittal spine mobility in both treatment groups compared to baseline ( $p < 0.05$ ). There was not a statistically significant difference between Tenaprost and Nimulid in their effect on sagittal spine mobility at baseline, 10 and 20 days of treatment.

Lower back muscle spasm by treatment arm is presented in table II. A larger percent of patients in the Tenaprost group had lower back muscle spasm at baseline, compared to the Nimulid group, but the difference was not statistically significant. After 10 and 20 days of treatment, paravertebral muscle spasm was reduced in both treatment groups compared to baseline. However, compared to baseline, lower back muscle spasm was statistically significantly lower ( $p < 0.05$ ) in the group treated by Tenaprost for 20 days.

The effectiveness of Tenaprost and Nimulid in the treatment of low back pain and knee osteoarthritis was evaluated by both physicians and patients at the end of the treatment (Tab. III). In the Nimulid group, the percentage of responders compared to the Tenaprost group was significantly greater according to both patients' (82.1% vs. 65.5%) ( $p = 0.001$ ) and physicians' evaluation (82.1% vs. 69%) ( $p = 0.001$ ). In the Tenaprost group, the percentage of responders was statistically significantly higher only according to physicians evaluation ( $p = 0.041$ ).

There were no serious adverse events which would result in treatment withdrawal in the Tenaprost or the Nimulid groups. Three patients (one in Tenaprost and two in Nimulid group) did not complete the study due to personal reasons independent from the drug use. The adverse events recorded in the Tenaprost group were nausea (3.3%), abdominal pain (3.3%) and headache (3.3%), while the Nimulid group reported abdominal pain (3.2%) and vertigo (3.2%). There were no statistically significant differences between the two treatment groups for any adverse events ( $p = \text{NS}$ ).

**Table III** - Patients' and investigators' evaluation of the efficacy of treatment at the end of the trial (20 days after the beginning of treatment) (N=57).

|  | Patients' evaluation (N=57) |           |           | Investigators' evaluation (N=57) |           |           |
|--|-----------------------------|-----------|-----------|----------------------------------|-----------|-----------|
|  | better                      | the same  | worse     | better                           | the same  | worse     |
| Tenaprost (n=29)   | 19 (65.5%)<br>p=0.095       | 8 (27.6%) | 2 (6.9%)  | 20 (69%)<br>p=0.041              | 7 (24.1%) | 2 (6.9%)  |
| Nimulid (n=28)   | 23 (82.1%)<br>p=0.001       | 2 (7.1%)  | 3 (10.8%) | 23 (82.1%)<br>p=0.001            | 2 (7.1%)  | 3 (10.7%) |
| Valid percentages are given, i.e. missing data are not included. |                             |           |           |                                  |           |           |

## DISCUSSION

In our study, Tenaprost and Nimulid tablets at a daily dose of 200 mg for 20 days were an effective analgesic therapy in the treatment of low back pain and knee osteoarthritis. They showed similar analgesic effects measured by VAS and by the knee sensitivity to palpation. After 20 days of treatment, pain was reduced for 32.9% and 42.3% in the Tenaprost and Nimulid group respectively. Similar percentage of pain reduction (40.5%) was obtained when nimesulide was applied in the treatment of knee osteoarthritis in the study of Fioravanti et al. (16). None of these two nimesulide formulations had an effect on knee circumference. After 20 days of treatment Tenaprost and Nimulid demonstrated similar efficacy in the improvement of sagittal spine mobility in those patients with low back pain. Several differences between the effects induced by these copies of nimesulide have been found (for example LT, PVM spasm and the use of paracetamol as a rescue drug), which indicates that Tenaprost might be slightly more effective in the treatment of low back pain. However, based on patients' and investigators' evaluation, these differences were not of clinical significance.

The differences in safety of these two formulations of nimesulide were not observed in our study. The widespread use of NSAIDs is increasing with age with the total prevalence of prescription at the age of 65 of 10-15%. The most common adverse events are gastrointestinal adverse events ranging from dyspepsia to life threatening conditions such as per-

foration and hemorrhage. As a selective COX-2 inhibitor, nimesulide has the relatively rare propensity to produce severe gastrointestinal adverse reactions compared to other nonselective NSAIDs (17). In our study, although used in older patients, both Tenaprost and Nimulid were well tolerated and have not induced serious adverse events which would require withdrawal of therapy. There was not a statistically significant difference in the frequency of predominantly mild adverse effects between Tenaprost and Nimulid.

Based on our results, we could conclude that Tenaprost was the more effective treatment option for pain management in low back pain than Nimulid. In the treatment of knee osteoarthritis, these two generic copies of nimesulide were equally effective. The safety profile of both nimesulide forms was similar, and the most common adverse effects were mild and with similar rate in both treatment groups. Price per daily dose is a relevant parameter for making a choice between these two formulations in routine clinical practice. However, regulations regarding drug bioequivalence criteria should be met for drug marketing authorization submission.

## ACKNOWLEDGMENTS

*This work was supported by a grant from Panacea Biotec Ltd., India. We gratefully acknowledge the contribution of Dr. Dragica Maksimovic, Dr. Mirjana Stanisic, Dr. Viktorija Savic, Dr. Slobodanka Djordjevic-Kontic and Dr. Snezana Novkovic for their assistance with the data collection.*

## SUMMARY

**Background:** Two generic bioequivalent copies of the same drug sometimes do not achieve therapeutic equivalence. This may produce adverse events in clinical practice if the therapeutic index of that drug is narrow.

**Objective:** To compare the efficacy and safety of two generic copies of nimesulide Nimulid (N) and Tenaprost (T).

**Methods:** 60 out-patients with symptomatic low back pain or knee osteoarthritis were randomized to take T or N (100 mg 2 x/day for 20 days) in a prospective double-blinded randomized phase four clinical trial conducted at the Institute of Rheumatology, Belgrade, Serbia. Pain was evaluated by VAS. Paravertebral muscle spasm (PVM), sagittal mobility, and the Lasegue's test (LT) were estimated in low back pain. In knee osteoarthritis, knee circumference, motion, and knee tendons sensitivity (KTS) to palpation were assessed. Adverse events reported by the patients, or observed by the investigators were recorded.

**Results:** T and N significantly reduced pain levels in patients with low back pain and knee osteoarthritis ( $p < 0.001$ ) as well as knee circumference and KTS to palpation ( $p < 0.05$ ). Compared to N, T showed slightly better effects on the Lequesne functional index ( $p < 0.05$ ) and PVM spasm in patients with lower back pain, but that was not of clinical relevance. Tolerability of T and N was good.

**Conclusion:** T and N are equally effective and safe forms of nimesulide for pain management in low back pain and knee osteoarthritis. Price per daily dose is a relevant parameter for making a choice. However, regulations regarding drug bioequivalence criteria should be met for drug marketing authorization submission.

**Parole chiave** - Equivalenza terapeutica, nimesulide, farmaci generici, dolore lombare, artrosi del ginocchio.

**Key words** - Therapeutic equivalency, nimesulide, generic copies, low back pain, knee osteoarthritis.

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