2 Study Synopsis

Sponsor:	HEXAL AG Industriestraße 25 83607 Holzkirchen Germany Phone: ++49-(0)8024-908-0 Fax: ++49-(0)8024-908-1475	
Investigational product:	Diclo 150 HEXAL	
Active ingredient:	Diclofenac sodium	
Title of study:	Multi-center, double-blind, double-dummy, controlled, randomized phase III study on the tolerability and efficacy of Diclofenac Sodium 150 mg o.d. in comparison to Voltaren® 50 t.i.d. and Voltaren® Dispers t.i.d. in patients with osteoarthritis of the hip, knee or fingers over a treatment period of two weeks	
Study centers:	Recruited: 177 study centers in 4 countries (Germany: 120, Latvia: 1, Lithuania: 6, Romania: 50), Active: 132 study centers in 4 countries (Germany: 79, Latvia: 1, Lithuania: 6, Romania: 46), see appendix 16.1.4	
Investigators:	One main investigator per center, see appendix 16.1.4	
Publication:	None	
Study period:	Date of first enrolment April 19, 2005	Date of last completed September 26, 2005
Study phase:	Phase III	
Objectives:	Evaluation of efficacy and tolerability of Diclo 150 HEXAL in the treatment of osteoarthritis of the hip, knee or fingers as compared to Voltaren® Dispers and Voltaren® 50	
Methodology:	Prospective, multi-national, multi-center, randomized, double-blind, double-dummy study, with three parallel treatment groups	
Number of patients:	Planned: 1500	Analyzed: 1501
Diagnosis and main criteria for inclusion:	Diagnosis: Osteoarthritis of the hip, knee or fingers Main criteria for inclusion: • Between 18 and 75 years of age • Out-patient able to perform daily routine • Clinically confirmed localised idiopathic osteoarthritis of the hip, knee or fingers according to ACR guidelines • Patient's overall assessment of pain ≥ 40 mm (VAS) at screening (visit 1) and at baseline (visit 2) • Patient requiring NSAID therapy for at least 2 weeks	

	Main criteria for exclusion: • Acute trauma • ACR class IV • Generalized idiopathic or seconday osteoarthritis • Congenital or developmental disease • Calcium deposition disease • Other bone and joint disorders • Other diseases (as specified in the protocol) • Intake of anti-inflammatory drugs • Intake of NSAIDs during the last 3 to 7 days prior to baseline (as specified in the protocol) • Intake of analgesics during 12 hours prior to baseline
Test product / comparators:	Test product: Diclo 150 Hexal (modified release tablet) Reference product 1: Voltaren® Dispers (dispersable tablet) Reference product 2: Voltaren® 50 (enteric coated tablet)
Dose:	Diclo 150 HEXAL: 1 tablet daily Voltaren® Dispers: 3 tablets daily Voltaren® 50: 3 dragees daily Daily dose equal to 150 mg diclofenac sodium for all treatment groups
Mode of administration:	Orally
Batch nos.:	Collective batch no.: 050116
Duration of treatment:	14 days

Criteria for evaluation:

Efficacy

Primary efficacy variable

- Change of the patient's overall assessment of pain in the target joint ("global pain") between day 0 and day 14 (VAS)

Secondary efficacy variables

- Change of total score of WOMAC® Osteoarthritis Index between day 0 and day 14 (hip and knee only)
- Change of total score of Dreiser's functional index between day 0 and day 14 (fingers only)

Other variables related to efficacy

- Assessment of overall efficacy at the final visit by both the investigator and the patient
- Assessment of general well-being at the final visit by the patient

Safety

- Adverse events (AEs) and adverse drug reactions (ADRs)
- Gastrointestinal AEs (GI-AEs) and gastrointestinal ADRs (GI-ADRs) of special interest

- Cardiovascular AEs (CV-AEs) and cardiovascular ADRs (CV-ADRs)
- Serious AEs (SAEs) and serious ADRs (SADRs)
- Safety laboratory assessments (hematology and clinical chemistry)
- Vital signs and physical examination
- Assessment of overall tolerability at the final visit by both the investigator and the patient

Statistical methods:

A non-inferiority test for Diclo 150 HEXAL as compared to Voltaren® (pooled data from both Voltaren® groups) with respect to the primary efficacy variable was carried out as the confirmatory statistical analysis. The non-inferiority margin was set to $\Delta = 7$ mm in the protocol. The per-protocol (PP-EFF) data set was used for primary analysis. A secondary (supportive) analysis was carried out for the intention-to-treat (ITT-EFF) data set. Analysis of covariance (ANCOVA) was applied including treatment group and location (target joint) as factors and the baseline value (day 0) as a covariate in the statistical model.

Exploratory non-inferiority testing was carried out for Diclo 150 HEXAL as compared to Voltaren® for various subgroups defined by the two Voltaren® preparations, individual target joints and participating country, respectively.

Confidence intervals were calculated for the incidence rates of the adverse event and adverse drug reaction categories of interest (e.g. gastrointestinal, cardiovascular) and exploratory significance tests were provided for the differences between Diclo 150 HEXAL and the two Voltaren® treatment groups.

Summary – Conclusions

Efficacy results:

Mean baseline values of global pain were ranging from 67.1 mm (Voltaren® Dispers) to 68.4 mm (Voltaren® 50). The mean changes from baseline after two weeks of treatment were -38.8 mm for Diclo 150 HEXAL, -38.1 mm for Voltaren® Dispers and -39.6 mm for Voltaren® 50. For the pooled Voltaren® data the mean decrease was -38.9 mm, which was practically identical with the result achieved for Diclo 150 HEXAL. The 95% confidence interval for the treatment difference ranged from -2.3 mm to 2.7 mm. Because the upper limit was smaller than the predefined non-inferiority margin (7 mm), non-inferiority of Diclo 150 HEXAL as compared to Voltaren® was statistically proven at the $\alpha = 2.5\%$ level.

The result of the confirmatory efficacy analysis, which was carried out for the PP-EFF data set, was supported by the analysis based on the larger ITT-EFF data set.

The secondary efficacy criteria did not exhibit any relevant treatment differences. This provides additional support for the non-inferiority result obtained for the primary efficacy criterion.

Safety results:

The percentage of patients with treatment related adverse events (ADRs) was 17.7% for Diclo 150 HEXAL, 13.8% for Voltaren® Dispers and 13.9% for Voltaren® 50. The incidence rate of gastrointestinal adverse drug reactions (GI-ADRs) of special interest (i.e. referring to the part of the body between oesophagus and anus) was 13.7% for Diclo 150 HEXAL, 10.2% for Voltaren® Dispers and 10.7% for Voltaren® 50.

Only 3 patients (2 in the Voltaren® Dispers group and 1 in the Voltaren® 50 group) had AEs that were classified as serious (SAEs) and a total of 18 AEs (5 in the Diclo 150 HEXAL group) were of severe intensity. There were no cases of *peptic ulcer, gastrointestinal bleeding* or *gastrointestinal perforation.*

Diarrhoea and *gastritis* appeared more often in the Diclo 150 HEXAL group than in each of the Voltaren® groups, whereas *abdominal pain* and *nausea/vomiting* were much more prevalent under Voltaren®.

There was considerable interaction between study drug and location of the osteoarthritis with respect to the incidence rates of adverse drug reactions. When patients with target joint hip are considered, the lowest incidence rates of ADRs and GI-ADRs of special interest were observed in the Diclo 150 HEXAL group. For osteoarthritis of the knee Voltaren® 50 came off best and Voltaren® Dispers had the lowest incidence rates in patients with target joint fingers.

Differences in incidence rates occurred also with respect to the participating countries. When the pooled data from the three Eastern European countries (Romania, Lithuania and Latvia) are considered, there are practically no differences in incidence rates of ADRs and GI-ADRs between treatment groups. In Germany, however, the number of patients with adverse drug reactions was comparatively higher in the Diclo 150 HEXAL group.

None of the secondary safety criteria provided indication to any relevant differences between treatments with respect to safety and tolerability.

Conclusions:

Diclo 150 HEXAL is a once daily diclofenac formulation, which has the advantage of increased patient compliance as compared to the three times daily administration of the investigated reference products Voltaren® Dispers and Voltaren® 50. Considering the large sample size in this study and the robustness of the results, it can clearly be concluded that Diclo 150 HEXAL is not inferior with respect to efficacy to any of the two Voltaren® preparations in the treatment of osteoarthritis of the hip, knee or fingers.

There was no indication to any cardiovascular risk for the three study treatments. On the other hand it was observed, that there were more general and also more gastrointestinal drug reactions in the Diclo 150 HEXAL group than in any of the two Voltaren® groups. Considering the fact, however, that no serious or otherwise significant or unexpected adverse drug reactions occurred, and that the incidence rates differed considerably between the locations of the osteoarthritis as well as between the participating countries, attenuates the relevance of these findings. In particular there was no difference in incidence rates of adverse drug reactions between treatment groups in the Eastern European countries. Relating the safety results of this study to published data of comparable trials suggests that the incidence rates observed in the Eastern European countries are more likely to reflect the safety profile of Diclo 150 HEXAL.

Date of report:	December 20, 2006