SYNOPSIS

Name of Sponsor/ Company: Gebro Pharma GmbH	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Seractil® ready oral suspension		
Name of Active Ingredient: Dexibuprofen		

Title of Study:
Population pharmacokinetic/pharmacodynamic and tolerability clinical trial in patients suffering from acute post-operative pain

Investigators:
Sites in Austria
Site 1: Prof. Christoph Male
Site 2: Prim. Univ. Prof. Dr. Robert Rogy
Site 3: Prim. Univ. Prof. Dr. Karl Franz Zwiauer
Site 4: Prim. Univ. Doz. Dr. Christian Huemer
Site 5: Univ. Prof. Prim. Dr. Wolfgang Sperl
Site 6: Prim. Univ. Prof. Dr. Robert Birnbacher
Site 7: OA Univ. Doz. Dr. Andreas Zoubek

Sites in Poland:
Site 8: Dr. Marek Migdał, MD, PhD
Site 9: Prof. Andrzej Piotrowski, MD, PhD

Study Centre(s):

Sites in Austria
Site 1:
Universitätsklinik für Kinder- und Jugendheilkunde,
Medizinische Universität Wien,
1090 Wien

Site 2:
KH der Barmherzigen Brüder Wien
Chirurgische Abteilung
Große Mohrengasse 9
1020 Wien

Site 3:
Allgemeines Öffentliches Krankenhaus der Landeshauptstadt St. Pölten
Abteilung für Kinder- und Jugendheilkunde
Propst-Führer-Straße 4
3100 St. Pölten

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Site 4:
Abteilung für Kinder- und Jugendheilkunde
Landeskrankenhaus Bregenz
6900 Bregenz

Site 5:
Universitätsklinik für Kinder- und Jugendheilkunde (Kinderspital Salzburg)
Salzburger Landeskliniken (SALK)
Müllner Hauptstraße 48
5020 Salzburg

Site 6:
Landekrankenhaus Villach
Nikolaigasse 43
9500 Villach

Site 7:
St. Anna Kinderspital
Kinderspitalgasse 6
1090 Wien

<u>Sites in Poland:</u>
Site 8:
Instytut "Pomnik – Centrum Zdrowia Dziecka"
Klinika Anestezjologii I Intersywnej Terapii
04-730 Warszawa, al. Dzieci Polskich 20

Site 9:
SPZOZ Uniwersytecki Szpital Kliniczny Nr 4 im. Marii Konopnickiej Uniwersytetu Medycznego w Łodzi
Oddział Kliniczny Intersywnej Terapii I Anestezjologii

91-738 Łód, ul. Sporna 36/50

Publication (reference):
none

Studied period (years): 11.06.2006	**Phase of development:**

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(date of first enrolment) 22.06.2010 (date of last completed)	Phase III Study	

Objectives: To test bioequivalence between adults and children according to CPMP/EWP/QWP/401/98 guideline and to test non-inferiority of the investigational medicinal product (Dexibuprofen) versus an active control (ibuprofen) concerning pain relieve according to CPMP/ICH/363/96 guideline.

Methodology: Prospective, randomised, multi-centre, open-label, analyst-blinded, multi-national, controlled, parallel-group, comparative clinical trial of phase III

Number of patients (planned and analysed):

planned:

64 children and 32 adults - *Austria* (pharmacokinetic/pharmacodynamic)

96 children (pharmacodynamic) – *Austria and Poland*

In total 160 children and 32 adults are invited to participate

analysed:

screened: 145 in total; 41 (2-4 years), 66 (5-11 years), 37 (adults), 1 age unknown

excluded: 43 in total; (2-4 years), (5-11 years), (adults)

randomised: 102 in total; 22 (2-4 years), 42 (5-11 years), 37 (adults), 1 age unknown

patients who didn't receive any medication: 6 in total; 3 (2-4 years), 2 (5-11 years), 0 (adults)

patients who received medication: 96 in total; 19 (2-4 years), 40 (5-11 years), 37 (adults)

of these received Dexibuprofen: 53 in total; 10 (2-4 years), 22 (5-11 years), 21(adults)

of these received Ibuprofen: 43 in total; 9 (2-4 years), 18 (5-11 years), 16 (adults)

Diagnosis and main criteria for inclusion:

Diagnosis: acute post-operative pain

Inclusion criteria: male or female patients; age between 2 and 11 years (children, Subgroups: 2-4 years and 5-11 years) and 18 and 55 years (adults), body weight between 12 kg and 121 kg (> 11 kg and < 122 kg), written informed consent/assent (parents and

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children, adults); acute post-operative pain (at least moderate) – pharmacodynamic patients only, operation (surgery).

Test product, dose and mode of administration, batch number:
Dexibuprofen ready oral suspension, strength: 100 mg/5 ml, single oral dose 5 mg/kg body weight

Manufacturer: Gebro Pharma GmbH, Austria

Batch number: 059502, 420710

Duration of treatment:
1-2 clinical trial days per patient

Reference therapy, dose and mode of administration, batch number:
Ibuprofen liquid formulation (Nureflex®), strength: 100 mg/5 ml, single oral dose 10 mg/kg body weight

Marketing authorisation holder: Booths Healthcare Deutschland, Hamburg
obtained from commercial source in Austria
Batch number: 736601, 64D

Criteria for evaluation:
Analyses were done on the results for KUSS pain scale investigating the change of KUSS from baseline (KUSSBL) to any time point after baseline as time weighted (tw) Pain Intensity Differences (PIDtw). In the same way the time weighted PIDs were built for the FACE pain scale for each time point post baseline (15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6 hours).
Total pain relief (TOTPAR) was analyzed also as time weighted measurement at each time point post baseline (15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6 hours).
Sums over all time points were built for the time weighted PIDs of KUSS pain scale and FACE pain scale as well as for the time weighted total pain reliefs (KUSS_SPIDtw, FACE_SPIDtw; TOTPARtw).
For PIDs of KUSS and FACE pain scale the peak values and time of peak were analyzed as well as for the total pain relief (TOTPAR). As a measurement of theoretical maximum TOTPAR the parameter %TMT was investigated.

Efficacy:
Results KUSS-pain scale Pain Intensity Difference (PID) time weighted and sum (SPID)
The mean reduction (negative change) of KUSS compared to baseline appears very similar in both groups with slight shifts to the right in the confidence intervals for mean difference (less reduction for Dexibuprofen) at 4 hours post baseline and a left shift (stronger reduction for Dexibuprofen) for the last time point (6h). Time weighted sum over all time points showed nearly identical mean values where median value was higher in the Dexibuprofen-group.
Differences between treatments did not reach significance at any time point. ANCOVA models showed no treatment effect at any time point. KUSS at baseline was a significant covariate at any time point and Age showed influence at time points 45 minutes and 1 hour post baseline.

Results Face-pain scale Pain Intensity Difference (PID) time weighted and sum (SPID)
The mean reduction (negative change) of FACE compared to baseline appears very similar in both groups with a shift to the right in the confidence intervals of mean difference (less reduction for Dexibuprofen) at the early time points (15m, 30m, 45m). At the later time points starting at 1.5h a left shift (stronger reduction for Dexibuprofen) could be observed except for time point 4h. Time weighted sum over all time points also showed a slight left shift of the confidence interval indicating stronger reduction by Dexibuprofen.
Differences between treatments did not reach significance at any time point. ANCOVA models showed no significant treatment effect at any time point, although p-values for time points 15m and 45m were rather small. FACE at baseline was a significant covariate at any time point and Age showed influence at time point 1.5h. No treatment-effect could be seen for the time weighted sum of PID (FACE_SPIDtw), where FACE at baseline was significant also.

Results Total Pain Relief (TOTPAR) time weighted and sum (TOTPAR tw)
Mean and median TOTPAR appears very similar in both groups. Shifts of the confidence intervals for the mean difference were observed rather to the left (except time points 2h, 6h) speaking for lower TOTPAR-values in the Dexibuprofen group. These left shifts were also seen for the time weighted sum over all time points (TOTPARtw). Differences between treatments did not reach significance at any time point. ANCOVA models showed no significant treatment effect at any time point. KUSS at baseline showed influence only at time point 15m but at none of the other time points and sums, neither did Age.

Results Peak Values and Time of Peak for PID of KUSS- and FACE-pain scale and TOTPAR
Mean and median values for KUSS PID peak value and time appeared similar in both treatment groups. A slight shift to the right could be seen for the confidence interval for

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mean difference in time, meaning that KUSS PID peak value appeared later in the Dexibuprofen group. Differences between treatments did not reach significance for any variable. There was no significant treatment effect on KUSS PID peak time (h) in the ANCOVA model. Age seemed to have an influence on peak time.
Mean and median values for FACE PID peak value and time appeared similar in both treatment groups. Differences between treatments did not reach significance for any variable. In ANCOVA models there was no significant treatment effect on FACE PID peak value nor on peak time (h). FACE value at baseline was significant in both models.
Mean and median values for Total Pain Relief (TOTPAR) peak value and time appeared similar in both treatment groups. Differences between treatments did not reach significance for any variable. ANCOVA models showed no significant treatment effect on Relief peak value nor on peak time (h).

Results percentage theoretical maximum TOTPAR (%TMT)

The confidence interval for mean difference showed a shift to the left (lower values for Dexibuprofen group). Differences between treatments did not reach significance. ANCOVA model showed no significant treatment effect.

Results Pharmacokinetic Analysis
Due to the fact that the trial was terminated prematurely and there were not enough adequate data especially for the pharmacokinetic part the results (Cmax, tmax, AUC_{0-t}, AUC_{0-inf}) are listed here only and not statistically evaluated.

Safety
During the study the *(Sub)Investigators* reported that 5 patients presented a total of 5 non-serious adverse events.

During the treatment period for the test product *Dexibuprofen*, there were no serious adverse events but 4 non-serious adverse events reported by the Investigators. There were 3 mild, 1 moderate and no severe adverse events reported. Overall, 0 events were considered to be of probable relationship, 1 event was considered to be of possible relationship, 2 events were considered to be of unlikely relationship and 1 event was considered to be not related to the trial medication.

During the treatment period for the reference product *Ibuprofen*, there were no serious adverse events but 1 non-serious adverse event reported by the Investigators. The Intensity of this AE was reported as mild and the relationship as “not related” to the trial medication.

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Data Entry process showed 4 further Adverse Events detected by *Data Entry Persons/Data Manager*. All findings were submitted by Data Manager as "Serious Non Compliances" to Trial Manager. These Adverse Events are listed here in detail:

Additional Adverse Events "Dexibuprofen 2% Solution"

CRF No.	Adverse Event	Case SOC	Description
101	Vomiting	Gastrointestinal Disorders	On the back side of page 35/CRF there is an AE noted.
623	Tachycardia	Cardiac Disorders	There is a second Adverse Event noted on a second AE-Form in the CRF, but only one page was filled in.

Additional Adverse Events "Nureflex®" (Ibuprofen 2% Solution)

CRF No.	Adverse Event	Case SOC	Description
105	Vomiting	Gastrointestinal Disorders	Vomiting after application of test substance as noted on the back side of page 17/CRF.
113	Fever	General Disorders and Administration Site Conditions	On page 39 (day 2)/CRF it is noted, that patient had fever. Concomitant Medication: Augmentin.

SUMMARY – CONCLUSION:

EFFICACY RESULTS: All parameters showed similar results for both treatments with slight shifts to the left or right of the confidence intervals of mean difference at a few time points, but no systematic deviations. Also ANCOVA models showed no significant treatment effect for any parameter at any time point indicating that significant differences between treatments were never reached.
In summary analyses revealed very similar results for both treatments over all parameters.

SAFETY RESULTS: Both study treatments (Dexibuprofen/Ibuprofen) were well tolerated. The observed adverse events were not unexpected. There is no need for a re-assessment of risk/benefit evaluation of the substances.

CONCLUSION: This clinical trial was a multi-centre, randomized, analyst-blinded, parallel group trial of phase III to test bioequivalence between adults and children and to test non-

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inferiority of Dexibuprofen versus the active control Ibuprofen in patients suffering from acute post-operative pain. Due to serious study protocol deviations/violations and patient recruitment problems this study was terminated prematurely. Consequently no statistical evaluation could be calculated for the comparison of bioequivalence. The available data for efficacy do not indicate differences in pain relief between both treatment groups in the ITT population. Safety analysis revealed no unexpected adverse events; both study treatments were well tolerated.

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EudraCT project code: Gebro - III - 28 – 2

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