SYNOPSIS

Name of the Sponsor/Company: Gebro Pharma GmbH **Name of the finished product:** Dexibuprofen film coated tablets **Name of the active ingredient:** dexibuprofen	Individual study table referring to part <##> of the dossier Volume: Page:	(For National Authority Use Only!)
Title of the Clinical Trial:	Efficacy and Tolerability of Dexibuprofen Film Coated Tablets in Comparison to Ibuprofen in Children and Adolescents with Tonsillopharyngitis	
Protocol Number:	III/21.10	
EUDRACT Project Code:	Gebro – III-21-10	
EUDRACT Number:	2004-004267-30	
Investigator:	AT: Univ. Doz. Dr. Christian Huemer, Univ. Doz. Dr. Burkhard Simma, Univ. Prof. Dr. Karl Franz Zwiauer, Univ. Prof. Dr. Lothar-Bernd Zimmerhackl, Univ. Prof. Dr. Werner Zenz DE: Dr. Rudolf Kappes, Dr. Irmingard Tichmann-Schumann, Dr. Christoph Wittermann	
Publication (reference):	not determined	
Studied period:	Notification to Regulatory Authority: Aproval of Independent Ethics Committee: Date of first patient in: (Pat. No. # 154, Centre 1) Date of last patient out: (Pat. No. #419, Centre 8) Notification to Regulatory Authority (End of clinical trial):	24.06.2003 (AT) 24.03.2005 (DE) 14.08.2003 (AT) 17.02.2005 (DE) 16.09.2003 (AT) 17.12.2007 (DE) 25.02.2008 (AT/DE)
Phase of development:	phase III	
Objectives:	To compare the analgesic efficacy in the first 6 hours of a single oral dose of 100 mg dexibuprofen with 200 mg ibuprofen in children and 200 mg dexibuprofen versus 400 mg ibuprofen in adolescents with sore throat pain due to tonsillopharyngitis. To compare the overall effectiveness of dexibuprofen with ibuprofen during a 3 days follow-up treatment period in patients suffering from sore throat complaints due to tonsillopharyngitis. To evaluate and compare the tolerability profile of dexibuprofen and ibuprofen in children and adolescents	
Methodology:	Prospective, open-label, randomised, active-controlled, multi-centre, multi-national, multi-dose, parallel group comparative non-inferiority trial of phase III in 200 children and adolescents with tonsillopharyngitis	

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Number of patients planned:	N = 200 children and adolescents (100 per investigational medicinal product group and 100 per age class, 50 per treatment group/age class): 100 children (age 8-11 years) 100 adolescents (age 12-18 years)
Number of patients analyzed:	Screened: 373 Randomized: 200 Safety and Tolerability: 198 Efficacy: 197 ITT population: Efficacy: 188 PP population:
Diagnosis and main criteria for inclusion:	Diagnosis: Tonsillopharyngitis (ICD: J06.8) Inclusion criteria: male or female patients between 8 and 18 years of age, diagnosed tonsillopharyngitis (TPS score $\geq$ 4), acute sore throat pain (moderate, severe or extreme), written informed consent/assent (parents and children/adolescents); Exclusion criteria: patients previously sensitive to dexibuprofen or ibuprofen, to any other NSAID, or to any excipient of the products; patients in whom substances with similar action (e.g. aspirin or other NSAIDs) precipitate attacks of asthma, bronchospasm, acute rhinitis, or causal nasal polyps, urticaria or anioneurotic oedema; patients with active or suspected gastrointestinal ulcer or history of gastrointestinal ulcer (in the past 6 months); patients who have gastrointestinal bleeding or other active bleedings or bleeding disorders; patients with Crohn´s disease or ulcerative colitis, with severe heart failure, with severe renal dysfunction (GFR < 30 ml/min), with severely impaired hepatic function, with haemorrhagic diathesis and other coagulation disorders, or patients receiving anticoagulant therapy; pregnancy; connective tissue diseases such as e.g. lupus erythematosus and other autoimmune diseases; use of analgesic, antipyretic or anti-inflammatory drugs within the last 3 days prior to entry into the trial, regular use of concomitant treatment of drugs with pharmacological effects that may modify the results of the trial or use of cold medication within the past 4 hours, participation in an other clinical trial less than 30 days ago, simultaneous participation in an other clinical trial;
Test product 1, dose and mode of administration, batch number:	Dexibuprofen film coated tablets, strength: 100 mg, oral administration t.i.d. (200 mg divided in half) Batch number: 156204/404409/039701 Manufacturer: Gebro Pharma GmbH
Test product 2, dose and mode of administration, batch number:	Dexibuprofen film coated tablets, strength: 200 mg, oral administration t.i.d. Batch number: 156204/404409/039701 Manufacturer: Gebro Pharma GmbH

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Duration of treatment:	Single dose with 1 to 3 days follow-up	
Dosage:	Single dose and up to3 film coated tablets per day in follow-up phase	
Comparator product 1, dose and mode of administration, batch number:	Ibuprofen sugar coated tablets, strength: 200 mg, oral administration t.i.d. Batch number: 210543/10270574 Manufacturer: commercial source (Nycomed)	
Comparator product 2, dose and mode of administration, batch number:	Ibuprofen film coated tablets, strength: 400 mg, oral administration t.i.d. Batch number: 225052/225051/10275896 Manufacturer: commercial source (Nycomed)	
Duration of treatment:	Single dose with 1 to 3 days follow-up	
Dosage:	Single dose and up to3 film coated or sugar coated tablets per day in follow-up phase	
Escape Medication:	Paracetamol syrup 200 mg/5 ml Batch number: D02582/C27690/E37542/H06322 Manufacturer: commercial source (Ratiopharm)	
Permitted concomitant medication:	Antibiotic tonsillopharyngitis therapy, escape medication ($\geq$ 4 h after first drug intake, if appropriate)	
Prohibited concomitant medication:	None with analgesic, antipyretic or anti-inflammatory properties such as other NSAIDs besides the provided trial medication or corticoids as well as sulphonyl ureas, herbal remedies indicated for fever or sore throat pain, sore throat lozenges, sulphonamides, ticlopidin, decongestants containing antihistamines or corticoids.	
CRITERIA FOR EVALUATION **Efficacy:**	Primary efficacy criteria: Sum of pain intensity differences (SPID), time-weighted (0 to 4 hours) and total pain relief (TOTPAR), time weighted (0 to 4 hours). Co-primary efficacy criteria: Time-specific pain intensity difference (CPMP/EWP/612/00 Guideline 2002), number of responders (low assay sensitivity according to FDA Guidance for Industry, Guideline for the Clinical Evaluation of Analgesics, December, 1992), responder defined as $\geq$ 50% TMT [whereas %TMT = percentage theoretical maximum TOTPAR (Cooper 1991, McQuay et al 1995)] Secondary efficacy criteria: Time course analysis (time-specific pain intensity, time-specific relief scale), onset of analgesia [definition of time to onset: decrease of pain intensity by at least 50% for at least one hour according to VAS scale (for 50% as success, see McQuay et al 1995)], duration of analgesia (definition of duration: time from onset of 50% pain relief until the intensity of pain returns to baseline), peak effect, time to peak effect.	

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	Escape medication: number of patients with escape medication and time to escape medication (if more than 10% in each treatment group require rescue medication); SPID (0 to 6 hours), TOTPAR (0 to 6 hours), %maxTOTPAR (%TMT 0 to 4 hours), %maxTOTPAR (%TMT 0 to 6 hours), global assessment of effectiveness by patient and global assessment of efficacy by patient and investigator. <u>Follow-up criteria (day 1 to day3):</u> Baseline and every day, morning and evening prior to oral ingestion of investigational products time course analyses of pain intensity during swallowing, perception of swelling and perception of difficulty swallowing	
Safety:	Adverse events were monitored throughout the clinical trial. Additionally at final visit a global subjective assessment of tolerability by patient and investigator was performed	
Statistical methods:	Confirmatory analysis for proof of efficacy was a global test on the ensemble of primary criteria: $SPID_{0\text{-}4h}$ and $TOTPAR_{0\text{-}4h}$. The analysis was performed using the directional test of stochastic order within the framework of the non-parametric multivariate Wilcoxon-Mann-Whitney test of Wei and Lachin. If the test gave a statistically significant result, efficacy is proven as at least one of the single zero hypotheses cannot be true. The statistical significance of single criteria can also be tested in confirmatory way by testing each with full alpha, if the first global-test was statistical significant (close testing principle) (Lehmacher et al 1992). If non-inferiority has been proven a test for superiority or relevant superiority can be performed without adjusting alpha. After a significant result with SPID and TOTPAR, the time-specific intensity difference must undergo a confirmatory test again using the directional test of the Wei-Lachin procedure (see Thall and Lachin 1988, Rosenberger et al 1995, Kuhn and DeMasi 1999). Testing the differences with baseline corresponds to testing the interaction hypothesis (test of parallelism of time courses) in the classical ANOVA split plot analysis although the ANOVA test is unidirectional (omnibus) whereas the Wei-Lachin test is directional and thus more efficient if there is no crossing of the time courses. The next test was the test for non-inferiority for the number of responders. This test is just the test for non-inferiority using the confidence interval approach (alpha= 0.025, one sided) for the difference of proportions using the unconditional Barnard type Röhmel-Mansmann procedure (Röhmel and Mansmann 1999, Frick 2000). Secondary criteria data analysis: Time course analysis was performed using the Wei-Lachin procedure as described above. The peak effect was analysed using	

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	the Wilcoxon-Mann-Whitney procedure (Mann-Whitney measure of superiority with confidence interval). For time-to-event data (onset, duration, etc.) the median time is calculated using the Kaplan-Meier interpolation (this is recommended by the FDA Guideline DAAODP, 1994). The time points with/under escape or re-medication are regarded as informatively censored observations and they are replaced with imputation technique (last escape free value carried forward). Global assessments of efficacy are analysed using the Mann-Whitney estimator confidence interval.
SUMMARY – CONCLUSIONS	
Efficacy results:	The single doses of dexibuprofen and ibuprofen provided the expected profile of pain relief and body temperature decrease. In the present clinical trial in children and adolescents for dexibuprofen a significant faster time to peak pain intensity difference (p= 0.0067) and time to peak body temperature decrease (p= 0.0032) was demonstrated. Dexibuprofen yielded the peak effect after ~2.5 hours (2.40 hours resp. 2.57 hours). In contrast, ibuprofen yielded the peak effect after 3.1 or 3.3 hours, indicating a faster onset of maximal pharmacodynamic effect of ~ 30 to 45 minutes for dexibuprofen. This result is supported by the pain intensity reduction (VAS) of 1.4 cm after 30 minutes by dexibuprofen, which exceeds the clinically relevance of 1.o cm. In contrast ibuprofen had at this time point a pain intensity reduction of 1.0 cm which is borderline clinically relevant. This result is in accordance to data in adults (Dionne and McCullagh 1998, Kollenz et al 2008) and explained by the different solubility properties of the active substances. Interestingly, the faster onset of action is not accompanied by a shorter duration of action. The median duration of action for dexibuprofen was 5.025 hours and for ibuprofen 4.656 hours. The proportion of patients in each treatment group who achieved at least 50%maxTOTPAR was calculated using a valid equation. The number of patients with at least 50%maxTOTPAR (defined as responders) in the first 4 hours was then used to calculate relative benefit and number-needed-to-treat (NNT) for dexibuprofen versus ibuprofen in the double dose (McQuay and Moore 2006). In accordance to literature the responder rate in the present clinical trial was 49.50% in the ibuprofen group versus 53.51% in the dexibuprofen group. The calculated NNT is therefore 27.6 in favour for dexibuprofen. Single doses of dexibuprofen and ibuprofen provided a consistent decrease of pain intensity as assessed by pain intensity difference, pain relief and the summary measures SPID and TOTPAR. Absolute peak pain intensity measured by VAS and peak pain relief measured by VRS were equivalent as shown in the following two figures.

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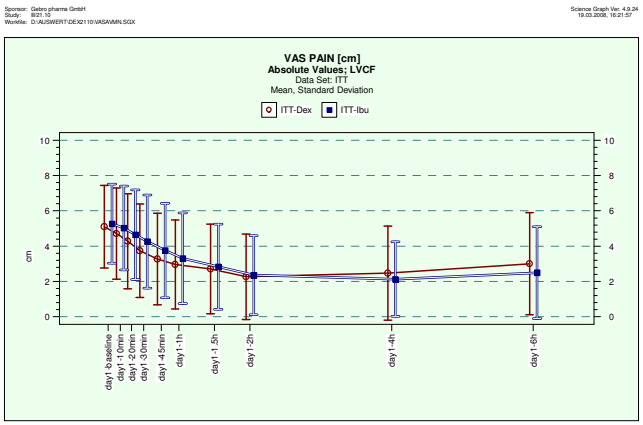
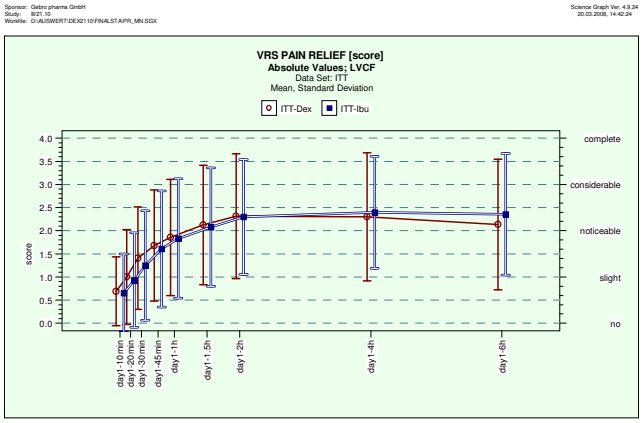
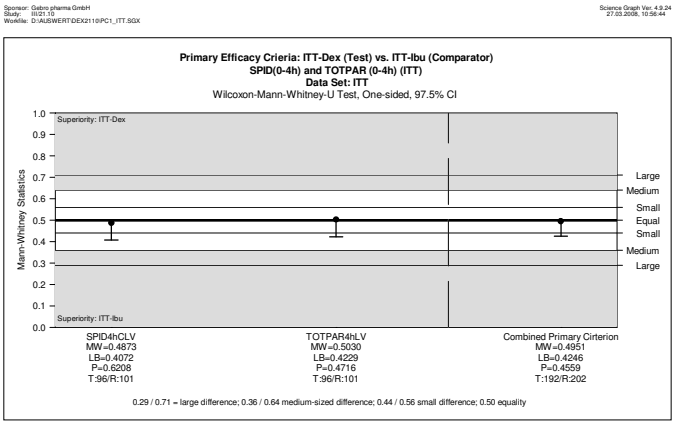




Non-inferiority of dexibuprofen vs. ibuprofen is proven by the primary criteria SPID and TOTPAR in children and adolescents.



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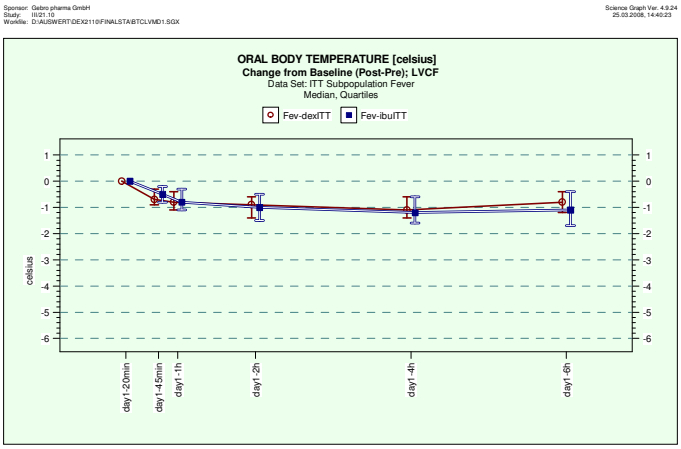
No significant differences, with exception of time to peak effect, in absolute antipyretic effect were demonstrated between dexibuprofen and ibuprofen.



Further, in the follow-up period patients in the dexibupropfen group retreated less frequently than in the ibuprofen group, represented by the lower total amount of voluntarily administered investigational medicinal products (dexibuprofen vs. ibuprofen at follow-up day2 1.92 vs. 2.12 and at follow-up day3 1.54 vs. 1.58 administrations/ patient).

A dose ratio of 0.5:1 of dexibuprofen versus conventional ibuprofen is established in adults. The dose ratio of 0.5:1 was theoretically expected in children and adolescents due to the development stages of the in metabolism of dexibuprofen involved organs in the investigated age classes. Equivalent analgetic and antipyretic efficacy was demonstrated in a dose ratio of 1:0.498 based on mg/kg body weight. Ibuprofen was administered in an average dose of 6.97 mg/kg body weight and dexibuprofen in an average dose of 3.47 mg/kg body weight. Therefore, the dose ratio of adults (dexibuprofen vs. ibuprofen 0.5:1) for the authorised indications can be transferred to children and adolescents and is confirmed also in this age classes by the present clinical trial. Furthermore, dexibuprofen showed a smaller variability in administered dose indicating a more precise dosing to children and adolescents due to the exclusion of R-ibuprofen.

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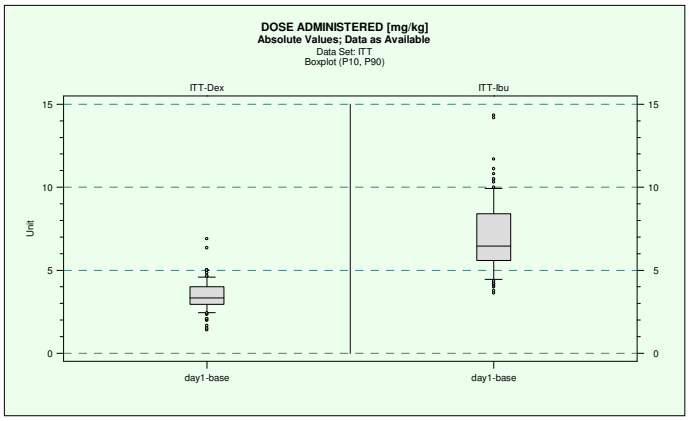

The stratified analyses according to age class showed no differences between ibupropfen and dexibuprofen in children as well as in adolescents.
Furthermore, the predefined secondary criteria as well as the predefined supportive and sensitivity analyses with raw data as available and with PP population confirm the results obtained by the confirmatory analyses (ITT data set).

Safety results:

For each patient the theoretical exposure to the investigational medicinal products was at maximum 4 days. The total exposure of the investigational medicinal products yielded in 302 treatment days or 907 tablet administrations. Interestingly more patients in the ibuprofen group retreated in the follow-up days. This result also supports the faster onset of action and the faster relieve of symptoms due to tonsillopharingitis in children and adolescents (dexibuprofen 1.48 days/patient vs. ibuprofen 1.57 days/patient). There were no safety issues raised by the pre and post clinical trial examinations. Treatment with the test investigational medicinal product dexibuprofen 100 mg or 200 mg resulted in 0 treatment related adverse events and treatment with the comparator investigational medicinal product ibuprofen 200 mg or 400 mg resulted in 0 treatment related adverse events. Further, the occurrence of related adverse events was rare in the present clinical trial. This was expected due to the single dose and short term follow-up trial design conditioned by the investigated self-limiting indication tonsillopharyingitis and the well tolerated investigational medicinal products in children and adolescents.

Conclusion

In this single dose with a 3 to 4 days follow-up period clinical trial, dexibuprofen was proven at least therapeutically equivalent to the well-established active substance ibuprofen in children and adolescents suffering from tonsillopharyngitis, with a faster onset of pharmacodynamic effect (analgetic and antipyretic effect) by the same duration of action.

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	Furthermore, the predefined supportive and sensitivity analyses with data as available and per protocol populations confirm the results obtained by the confirmatory analyses (ITT data set). In the present clinical trial the adult dose ratio of 0.5:1 (dexibuprofen vs. ibuprofen) is confirmed also in children and adolescents. This result was theoretically expected due to the development stages of the in metabolism involved organs in the investigated age classes. Equivalent analgetic and antipyretic efficacy was demonstrated in a dose ratio of 1:0.498 based on mg/kg body weight. Ibuprofen was administered in an average dose of 6.97 mg/kg body weight and dexibuprofen in an average dose of 3.47 mg/kg body weight. Therefore, the dose ratio of adults (dexibuprofen vs. ibuprofen 0.5:1) for the authorised indications can be transferred to children and adolescents. It can be concluded that dexibuprofen is an effective and well-tolerated short-term treatment of pain and fever related to acute tonsillopharyngitis in children and adolescents with the advantage of a faster onset of action but by not altering the duration of action in comparison to conventional ibuprofen.	
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