

# Relative bioavailability study of a generic effervescent tablet formulation of dexketoprofen and thiocolchicoside versus the originator 25 mg film coated tablet (dexketoprofen) and 8 mg capsule (thiocolchicoside)

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Received: 14 December 2021 / Accepted: 29 December 2021

**Aims:** The aim of this study was to evaluate the pharmacokinetic profiles and the relative bioavailability of dexketoprofen and thiocolchicoside of the test preparation (dexketoprofen / thiocolchicoside 25 mg / 8 mg effervescent tablet) in comparison with the reference preparations (Keral 25 mg film coated tablet, containing dexketoprofen trometamol equivalent to 25 mg dexketoprofen (Menarini International Operations Luxembourg S.A.) (R1) and Muscoril 8 mg capsule, containing 8 mg thiocolchicoside (Sanofi Aventis İlaçları Ltd. Şti.) (R2) under fasting conditions.

**Methods:** 25 healthy male subjects were enrolled in the study. Volunteers were hospitalised from the evening before drug administration (Day 0) until after the 24-hour blood sampling time on Day 2.

**Results:** 24 subjects completed the study. Relative bioavailability (AUCT/AUCR1) of dexketoprofen from the test preparation was 100.99 %; (AUCT/AUCR2) of 3-O-glucuronide of thiocolchicoside (aglycone) from the test preparation was 100.47 %; (C<sub>max,T</sub>/C<sub>max,R1</sub>) of Dexketoprofen from the test preparation was 122.59 %; (C<sub>max,T</sub>/C<sub>max,R2</sub>) of 3-O-glucuronide of thiocolchicoside (aglycone) from the test preparation was 111.43 %.

**Conclusions:** The relative bioavailability AUCT /AUCR of the test preparation compared with both reference preparations is comparable, as shown by the geometric mean ratios of 100.59 % (dexketoprofen) and of 98.20 % (3-O-glucuronide of thiocolchicoside (aglycone)).

**Keywords:** Dexketoprofen, Thiocolchicoside, Relative bioavailability study

## 1 INTRODUCTION

Dexketoprofen trometamol is the tromethamine salt of S-(+)-2-(3-benzoylphenyl) propionic acid, an analgesic, anti-inflammatory and antipyretic drug, which belongs to the non-steroidal anti-inflammatory group of drugs. It is designated chemically as: (S)-ketoprofen trometamol; 2-amino-2-(hydroxymethyl)-1,3-propanediol (S)-3-benzoyl-alpha-methylbenzeneacetate. The empirical formula of dexketoprofen trometamol is C<sub>20</sub>H<sub>25</sub>NO<sub>6</sub> and its molecular weight is 375.42 [1, 2]. It is highly soluble in water as an active enantiomer of rac-ketoprofen [3].

Thiocolchicoside (TCC) is a semi-synthetic derivative of colchicoside derived by substitution of a methoxy group with a thiomethyl group. This compound has been used for over 35 years as a myorelaxant in the treatment of painful muscle contractions in acute and chronic rheumatic conditions, in traumatology and especially in patients with acute low back pain. In addition, this drug possesses analgesic and anti-inflammatory properties observed in animal models and its good efficacy and its safety profile have been demonstrated clinically in several studies Investigation of the pharmacokinetics and bioequivalence of TCC, the

biological samples obtained must be assayed with a bioanalytical method able to specifically analyse TCC and its active metabolite 3-O-glucuronidated aglycone [4].

The mechanism of action of non-steroidal anti-inflammatory drugs is related to the reduction of prostaglandin synthesis by the inhibition of cyclooxygenase pathway. Specifically, there is an inhibition of the transformation of arachidonic acid into cyclic endoperoxides, prostaglandin G<sub>2</sub> (PGG<sub>2</sub>) and prostaglandin H<sub>2</sub> (PGH<sub>2</sub>), which produce prostaglandins prostaglandin E<sub>1</sub> (PGE<sub>1</sub>), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), prostaglandin F<sub>2a</sub> (PGF<sub>2a</sub>) and prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) and also prostacyclin PGB and thromboxanes (TxA<sub>2</sub> and TxB<sub>2</sub>). Furthermore, the inhibition of the synthesis of prostaglandins could affect other inflammation mediators such as quinine, causing an indirect action that would be additional to the direct action. Dexketoprofen has been demonstrated to be an inhibitor for cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) activities in experimental animals and humans [1].

### 1.1 Pharmacokinetics

After oral administration of dexketoprofen trometamol to humans, the maximum concentration ( $C_{\max}$ ) of dexketoprofen is reached at 30 min (range 15 to 60 min). When administered concomitantly with food, the area under the curve (AUC) does not change, however the  $C_{\max}$  of dexketoprofen decreases and its absorption rate is delayed [increased time to reach maximum concentration ( $t_{\max}$ )] [1].

It was reported that after oral administration, TCC is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1 hour (h) and with a terminal half-life of 2-6 h in summary of product characteristics of TCC 8 mg capsules. However, as Sutherland *et al.* recently pointed out, the analytical methods used in these studies, namely, radioimmunoassay (RIA) and gas chromatography coupled with mass spectrometry (MS) after enzymatic hydrolysis of TCC to its aglycone, 3 demethylthiocolchicine, do not differentiate the parent compound from potential pharmacologically active or inactive metabolites. Moreover, using a liquid chromatography-MS-MS method, Sutherland *et al.* found only traces of the parent drug in plasma of healthy volunteers given 8 mg orally (the recommended therapeutic dose) [5].

## 2 MATERIALS AND METHOD

25 healthy male subjects were enrolled in the study. 24 subjects, at an age between 19 and 46 years and with a body mass index between 19.1–28.7 kg/m<sup>2</sup>, completed the study. Volunteers were hospitalised from the evening before drug administration (Day 0) until after the 24-hour blood sampling time on Day 2.

### 2.1 Study design and volunteer selection

The present study detailed in this report was designed as a mono-centric, open-label, randomized, 2-period crossover single dose bioavailability study, and performed taking into consideration of the Committee for Medicinal Products for Human Use (CHMP) "Guideline on the Investigation of Bioequivalence", code CPMP/EWP/QWP/1401/98 Rev. 1/Cor\*\*, London, 20 January 2010 [6]. Based on an estimated variability in the range of 20–25 % for AUC<sub>0-t</sub> (Area Under the Curve, calculated from time zero until the last time point with quantifiable analyte concentrations) and  $C_{\max}$ , a total number of 24 completed cases was considered to be necessary and sufficient to allow a reliable determination of relative bioavailability.

The clinical trials were performed in accordance with the Declaration of Helsinki and current Good Clinical Practice (GCP) guidelines. Information was provided to all subjects, explaining the risks and benefits. Written consent was obtained before the study initiation. The protocol was approved by the Institutional Ethics Committee of Erciyes University, Kayseri, Turkey. The clinical part of the study was carried out by Gaziantep University Farmagen İKU Merkezi (Centre of GCP), Gaziantep, Turkey.

### 2.2 Inclusion criteria

Healthy, male volunteers between 18 to 55 years of age, body weight within 18.5–30 kg/m<sup>2</sup> of the ideal body weight in relation to height and age, blood pressure and heart rate within normal limits in a sitting position with no electrocardiogram (ECG) abnormality, without any systemic disease past or present will be included in the study.

### 2.3 Exclusion criteria

Volunteers were excluded from the study for the following reasons: history of hypersensitivity to

dexketoprofen, thiocolchicoside, and other related compounds; hepatitis, gall-bladder or liver diseases; patients with diseases which could interfere with the pharmacokinetic parameters of the drugs; treatment with any investigational drug (i.e., drug not yet approved) in the last 3 months before beginning of the trial; medication with drugs known to alter organs or systems such as barbiturates, phenothiazines, cimetidine, omeprazole etc. within the last 2 months; donation of blood or plasma within the last two months (60 days); alcoholic or methylxanthine-containing beverages or foods (coffee, tea, coke, chocolate) and fruit-juices from 2 days prior to each dosing until the last blood sampling; grapefruit and orange products from 7 days prior to the first dosing until the last sampling; smoking of more than 5 cigarettes or equivalent per day; alcohol or drug abuse; Human Immunodeficiency Virus-Ab (HIV-Ab) test positive or test on antibodies against Hepatitis C Virus (HCV) positive, positive drug screen or history of drug abuse (amphetamines, cannabinoids, benzodiazepines, cocaine, opioids, barbiturates) legal incapacity and/or other circumstances rendering the subject unable to understand the nature, scope and possible consequences of the study and evidence of an uncooperative attitude.

#### 2.4 Sample size

Based on an estimated intra-subject variability in the range of 20–25 % for target variables  $AUC_{0-t}$  and  $C_{max}$ , 24 subjects were considered to be necessary and sufficient for a reliable determination of relative bioavailability.

#### 2.5 Study medication and administration procedure

Both test (batch no. 03256) manufactured by Neutec İlaç San. Tic. A., Turkey.) and reference (Keral 25 mg Film Coated Tablet batch no: 14832 manufactured by Laboratorios Menarini, Barcelona, Spain and Muscoril 8 mg Capsule batch no:012114 manufactured by Zentiva Sağlık Ürünleri San ve Tic. A.Ş. Lüleburgaz Kırklareli Turkey) products were tested physically and chemically before starting the clinical trial and both were found to be appropriate.

Volunteers were hospitalised from the evening before drug administration (Day 0) until after the 24-hour blood withdrawal on Day 2. In randomised sequence, the volunteers received equivalent dosages of the test preparation and reference prepara-

tions together with 240 mL non-carbonated mineral water in each treatment period. Treatments were separated by a wash-out phase of 1 week.

After intake of dinner on the day of admission, the volunteers fasted over night for a minimum of 10 hours before drug administration and continued fasting for four hours following dosing. Thereafter a lunch was served. Subjects were not allowed to drink water from 1 h before until 1 h after administration, except that to be taken for the drug administration.

The subjects swallowed the study preparations together with 240 mL tap water in standing position. During the next two hours they had to remain sitting or standing, but not lying in bed (except for the experience of orthostatic discomfort). The correct and complete intake was supervised by a second medical professional and controlled by checking the oral and buccal cavity ('mouth check'). Effervescent tablets of the test preparation had to be dissolved first in 100 mL of tap water. After complete dissolution, the suspension was administered to the subjects. The residual was re-suspended in 140 mL of tap water and also administered to the subjects.

Vigorous physical activity will be prohibited at all times during confinement. The volunteers have to abstain from alcohol 2 days prior to each dosing until the last blood sampling of either period. Smoking will not be permitted during the periods of blood sampling. The chewing of chewing gum is not allowed on the day of dosing. No foods and beverages containing caffeine or other methylxanthines (coffee, tea, coke, chocolate) and fruit-juice from 2 days prior to each dosing until the last blood sampling will be allowed. No orange or grapefruit containing products from 7 days prior to the first dosing until the last sampling will be allowed.

All volunteers were provided with standardised meals throughout the hospitalisation period.

During each run, drug administration was performed in the morning of study day 1 at approximately 08:00 hours.

#### 2.6 Blood sampling

Blood samples were withdrawn from each subject in each period at the following time points: 0 h (pre-dose), 0.08 h, 0.17 h, 0.25 h, 0.33 h, 0.50 h, 0.67 h, 0.75 h, 1.00 h, 1.33 h, 1.67 h, 2.00 h, 2.50 h, 3.00 h, 4.00 h, 6.00 h, 8.00 h, 12.00 h, 16.00 h, 20.00 h and 24.00 hours post-dose.

At pre-determined time points given above approximately 7 mL of blood were taken by a short intravenous catheter. The blood samples (7 mL) were collected into tubes using  $K_2$ -ethylenediamine tetraacetic acid ( $K_2$ -EDTA) as anticoagulant. After sampling, blood samples were transferred into a water bath cooled with ice and remained there for not more than 20 minutes. Following centrifugation (3,000 g, 4–7°C, 10 min) the separated plasma from each sample was transferred into 3.5 mL labelled polypropylene storage tubes (two tubes per sample) and transferred to a deep-freezer (<-20°C) and kept there for a maximum storage period of 1 hour. At the latest after 1 hour, samples were transferred to <-70°C and stored there until transfer to the analytical facility Trident Bioanalytics Ltd.

### 2.7 Sample analysis

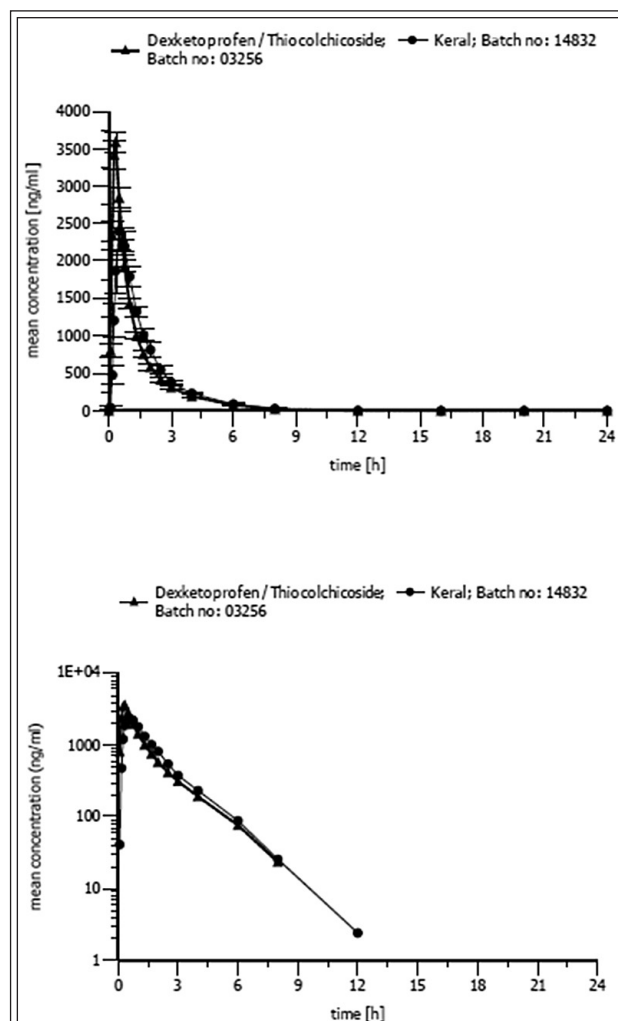
Analytical measurements were carried out on plasma levels of dexketoprofen and 3-O-glucuronide of thiocolchicoside (aglycone) with validated Liquid Chromatography–Mass Spectrometry (LC-MS/MS) methods with electrospray ionization ESI(-) for dexketoprofen (Trident Bioanalytics Ltd. SOP AN206) and electrospray ionization ESI(+) for 3-O-glucuronide of thiocolchicoside (aglycone) (Trident Bioanalytics Ltd. SOP AN205B). The analytical part was carried out in accordance with Good Laboratory Practices (GLP)-regulations. A lower limit of quantification of 50.76 ng/ml for dexketoprofen and 2.69 ng/ml for 3-O-glucuronide of thiocolchicoside (aglycone) was used during measurement of plasma samples with unknown concentrations. Mean relative deviations of QC-samples which represent the inter-assay accuracy (bias %) during measurement of study samples were calculated to be -0.54 % (Q-max), 1.25 % (Q-ave), 1.50 % (Q-med) and 1.40 % (Q-min) for dexketoprofen, 0.43 % (Qmax), 1.18 % (Q-ave), 1.12 % (Q-med) and 0.68 % (Q-min) for 3-O-glucuronide of thiocolchicoside (aglycone). Corresponding mean values of inter-assay precision (CV %) were 8.83 % (Q-max), 6.69 % (Qave), 6.80 % (Q-med) and 7.95 % (Q-min) for dexketoprofen, 2.51 % (Q-max), 2.63 % (Q-ave), 2.58 % (Qmed) and 5.03 % (Q-min) for 3-O-glucuronide of thiocolchicoside (aglycone).

### 2.8 Data analysis

The parameters  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  (Area Under the Curve, extrapolated to infinity),  $C_{max}$ ,  $t_{max}$ ,  $\lambda_z$  (elim-

ination rate constant),  $t_{1/2(\lambda_z)}$  (Terminal half-life calculated from  $\lambda_z$  according to  $t_{1/2} = \ln(2)/\lambda_z$ ) and  $AUC_{\%-\text{extrapol}}$  of dexketoprofen and 3-O-glucuronide of thiocolchicoside (aglycone) were determined with the program Phoenix WinNonlin V.6.4. The statistical treatment of pharmacokinetic study data corresponded with provisions given by the CHMP guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr\*\*, London, 20 January 2010 [6]. Analysis was performed as a valid case analysis according to the Pharmacokinetic and Statistical Plan, including all subjects with no major protocol violations and with all primary target variables available for measurement (per protocol subject set).  $AUC_{0-t}$  and  $C_{max}$  were primary target variables, whereas  $AUC_{0-\infty}$ ,  $t_{max}$ ,  $\lambda_z$  and  $t_{1/2(\lambda_z)}$  were considered as secondary target variables.

The relative bioavailability of the test preparation compared with both reference preparations



**Figure 1** Mean dexketoprofen plasma concentration/time profiles - linear ( $\pm$ SEM) and semilogarithmic plot ( $n = 24$ ).  $n =$  number of volunteers; SEM = standard error of mean

(R1, R2) was assessed from arithmetic and geometric mean ratios T/R1 resp. T/R2 for  $AUC_{0-t}$  and  $C_{max}$  of dexketoprofen and 3-O-glucuronide of thiocolchicoside (aglycone).

### 3 RESULTS

The plots of mean plasma concentration/time profiles for dexketoprofen and 3-O-glucuronide of thiocolchicoside (aglycone) is shown in [Figures 1](#) and [Figure 2](#), respectively. For dexketoprofen; pharmacokinetic results (arithmetic mean  $\pm$  s.d.;  $n = 24$ ) after test formulation (T) and reference product– Keral 25 mg film coated Tablet (R1)- dosing, the  $C_{max}$  was  $3,812.17 \pm 646.79$  ng/mL and  $3,259.05 \pm 739.31$  ng/mL; the  $AUC_{0-t}$  was  $4,182.57 \pm 945.04$  ng•h/mL and  $4,142.38 \pm 903.09$  ng•h/mL, respectively.

For 3-O-glucuronide of thiocolchicoside (aglycone), pharmacokinetic results (arithmetic mean  $\pm$  s.d.;  $n = 24$ ) after test formulation (T) and reference product– Muscoril 8 mg capsule (R2)– dosing the the  $C_{max}$  was  $58.85 \pm 22.42$  ng/mL and  $54.94 \pm 19.48$  ng/mL; the  $AUC_{0-t}$  was  $114.93 \pm 40.65$  ng•h/mL and  $113.91 \pm 31.54$  ng•h/mL respectively.

**Table I** Range of Values (test T vs reference R1) of dexketoprofen;  $n = 24$

	Primary pharmacokinetic parameters		Secondary pharmacokinetic parameters	
	$AUC_{0-t}$ [ng/mL•h]	$C_{max}$ [ng/mL]	$AUC_{(0-y)}$ [ng/mL•h]	$t_{max}$ [h]
T	2,261.71 – 5,787.15	2,564.34 – 4,815.09	2,389.77 – 5,931.53	0.17 – 0.75
R1	2,551.79 – 5,736.39	1,421.63 – 4,413.16	2,678.82 – 5,967.24	0.25 – 2.00

$AUC_{(0-\infty)}$  = Area Under the Curve, extrapolated to infinity;  $AUC_{(0-t)}$  = Area Under the Curve, calculated from time zero until the last time point with quantifiable concentrations;  $C_{max}$  = Maximum Concentration; h = hour; n = number of volunteers; R= reference; T = test;  $t_{max}$  = Time to reach maximum concentration

**Table II** Range of Values (test T vs reference R2) of 3-O-glucuronide of thiocolchicoside (aglycone);  $n = 24$

	Primary pharmacokinetic parameters		Secondary pharmacokinetic parameters	
	$AUC_{0-t}$ [ng/mL•h]	$C_{max}$ [ng/mL]	$AUC_{(0-y)}$ [ng/mL•h]	$t_{max}$ [h]
T	42.50 – 206.71	22.71 – 106.89	54.72 – 221.48	0.33 - 1.00
R2	62.62 – 177.08	19.84 - 88.21	73.84 – 187.00	0.50 – 3.00

$AUC_{(0-\infty)}$  = Area Under the Curve, extrapolated to infinity;  $AUC_{(0-t)}$  = Area Under the Curve, calculated from time zero until the last time point with quantifiable analyte concentrations;  $C_{max}$  = Maximum Concentration; h = hour; n = number of volunteers; R = reference; T = test;  $t_{max}$  = Time to reach maximum concentration

**Table III** Inter-Subject Coefficients of Variations

Inter-Subject Coefficients of Variation (n = 24) (inter-subject-cv)	Dexketoprofen:	3-O-Glucuronide of thiocolchicoside (aglycone):
$AUC_{0-t}$	22.59 % (T) 21.80 % (R1)	35.37 % (T) 27.69 % (R2)
$AUC_{(0-y)}$	22.06 % (T) 21.50 % (R1)	32.76 % (T) 26.46 % (R2)
$C_{max}$	16.97 % (T) 22.68 % (R1)	38.10 % (T) 35.46 % (R2)

$AUC_{(0-\infty)}$  = Area Under the Curve, extrapolated to infinity;  $AUC_{(0-t)}$  = Area Under the Curve, calculated from time zero until the last time point with quantifiable analyte concentrations;  $C_{max}$  = Maximum Concentration; n = number of volunteers; R = reference; T = test;  $t_{max}$  = Time to reach maximum concentration

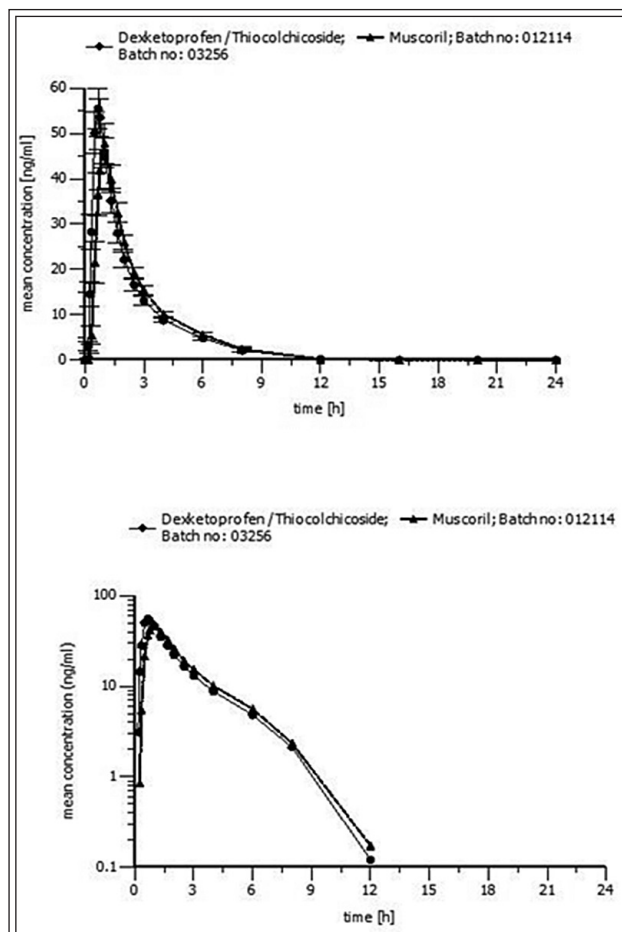
Range of values and inter-subject coefficients of variation for primary and secondary pharmacokinetic parameters of dexketoprofen and 3-O-glucuronide of thiocolchicoside (aglycone) are obtained as shown in [Tables I-III](#).

Relative bioavailabilities calculated from arithmetic means and geometric means of primary target variables  $AUC_{0-t}$  and  $C_{max}$  of dexketoprofen and 3-O-glucuronide of thiocolchicoside (aglycone) are calculated as shown in [Tables IV-V](#).

The pharmacokinetic results of dexketoprofen and thiocolchicoside (aglycone) are shown in [Tables VI-VII](#), respectively.

#### 3.1 Safety Results

In the course of the study, 2 adverse events were observed in 2 out of 25 enrolled subjects [dizziness (1/2), allergic reaction (1/2)]. The adverse event “dizziness” was of mild intensity. Dropout subject 017 experienced an allergic reaction of moderate intensity and was treated accordingly. All judgements on the drug relationship of the adverse events were recorded as “possible”. No severe or serious adverse events were reported.



**Figure 2** Mean plasma concentration/time profiles of 3-O-glucuronide of thiocolchicoside (aglycone) - linear ( $\pm$  SEM) and semilogarithmic plot ( $n = 24$ ).

$n$  = number of volunteers; SEM = standard error of mean

As to be expected for two single oral doses of 25 mg dexketoprofen and 8 mg thiocolchicoside, all treatments administered were well tolerated.

#### 4 DISCUSSIONS

Bioavailability is defined as the rate and extent to

**Table IV** Relative bioavailability of dexketoprofen from the test preparation

	Dexketoprofen
$(AUC_T/AUC_{R1})$	100.99 % (based on arithmetic means) 100.59 % (based on geometric means)
$C_{max,T}/C_{max,R1}$	122.59 % (based on arithmetic means) 118.83 % (based on geometric means)

AUC = Area Under the Curve;  $C_{max}$  = Maximum Concentration; R = reference; T = test

**Table V** Relative bioavailability of 3-O-Glucuronide of thiocolchicoside (aglycone) from the test preparation

	3-O-Glucuronide of thiocolchicoside (aglycone)
$AUC_T/AUC_{R2}$	100.47 % (based on arithmetic means) 98.20 % (based on geometric means)
$C_{max,T}/C_{max,R2}$	111.43 % (based on arithmetic means) 106.56 % (based on geometric means)

AUC = Area Under the Curve;  $C_{max}$  = Maximum Concentration; R = reference; T = test

which the active drug or therapeutic moiety thereof is absorbed from a medicinal product and becomes available at the site of drug action [7, 8]. According to the CHMP-guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr\*\*, London, 20 January 2010, "Investigation of Bioequivalence" [6], two medicinal products are bioequivalent if their bioavailabilities (rate and extent) after administration of the same molar dose are similar to such degree that their effects with respect to both efficacy and safety will be essentially the same. This requirement is fulfilled, if the 90 % confidence intervals of the  $AUC_{0-t}$  ratio and the  $C_{max}$  ratio are within a range of 80–125 %. In the present investigation no bioequivalence assessment had to be performed, rather the determination of relative bioavailability between test and reference preparations was the primary aim of the study.

Based on the obtained results, the relative bioavailability  $AUC_T/AUC_R$  of the test preparation (dexketoprofen / thiocolchicoside 25 mg / 8 mg effervescent tablet) compared with both reference preparations (Keral 25 mg film coated tablet (R1; dexketoprofen) and Muscoril 8 mg capsule (R2; thiocolchicoside) is comparable, as shown by the geometric mean ratios of 100.59 % (dexketoprofen; T/R1) and of 98.20 % (3-O-glucuronide of thiocolchicoside (aglycone); T/R2).

The relative bioavailability  $C_{max,T}/C_{max,R}$ , based on target variable  $C_{max}$  as a measure of the rate of drug absorption, is 118.83 % for dexketoprofen and 106.56 % for 3-O-glucuronide of thiocolchicoside (aglycone).

#### 5 CONCLUSIONS

Summarizing, the relative bioavailability between dexketoprofen / thiocolchicoside 25 mg / 8 mg effervescent tablet and Keral 25 mg Film coated tablet

**Table VI** Pharmacokinetic results (arithmetic mean  $\pm$  s.d.;  $n=24$ ) of dexketoprofen

Treatment	AUC <sub>(0-t)</sub> [ng/mL*h]	AUC <sub>(0-∞)</sub> [ng/mL*h]	C <sub>max</sub> [ng/mL]	t <sub>max</sub> [h]	λ <sub>z</sub> [1/h]	AUC % extrapol. [%]	t <sub>1/2(λ<sub>z</sub>)</sub> [h]
T: Dexketoprofen / thiocolchicoside 25 mg / 8 mg effervescent tablet batch no.: 03256	4,182.57 ±945.04	4,337.02 ±956.55	3,812.17 ±646.79	0.33 ±0.12	0.4557 ±0.0813	3.70 ±0.99	1.57 ±0.99
R1: Keral 25 mg film coated tablet Batch no: 14832	4,142.38 ±903.09	4,305.13 ±925.50	3,259.05 ±739.31	0.63 ±0.39	0.4671 ±0.0943	3.84 ±1.00	1.57 ±0.4

λ<sub>z</sub> = elimination rate constant; AUC<sub>%extrapol</sub> = percentage of the residual area extrapolated to time infinity in relation to the total area under the curve; AUC<sub>(0-∞)</sub> = Area Under the Curve, extrapolated to infinity; AUC<sub>(0-t)</sub> = Area Under the Curve, calculated from time zero until the last time point with quantifiable analyte concentrations; C<sub>max</sub> = Maximum Concentration; n = number of volunteers; R = reference, s.d. = standard deviation; T = test; t<sub>1/2(λ<sub>z</sub>)</sub> = Terminal half life calculated from λ<sub>z</sub> according to t<sub>1/2</sub> = ln(2)/ λ<sub>z</sub>; t<sub>max</sub> = Time to reach maximum concentration

**Table VII** Pharmacokinetic results (arithmetic mean  $\pm$  s.d.;  $n=24$ ) of 3-O-glucuronide of thiocolchicoside (aglycone):

Treatment	AUC <sub>(0-t)</sub> [ng/mL*h]	AUC <sub>(0-∞)</sub> [ng/mL*h]	C <sub>max</sub> [ng/mL]	t <sub>max</sub> [h]	λ <sub>z</sub> [1/h]	AUC % extrapol. [%]	t <sub>1/2(λ<sub>z</sub>)</sub> [h]
T: Dexketoprofen / thiocolchicoside 25 mg / 8 mg effervescent tablet batch no.: 03256	114.93 ±40.65	127.65 ±41.81	58.85 ±22.42	0.66 ±0.17	0.3039 ±0.07	10.85 ± 5.09	2.40 ±0.57
R2: Muscoril 8 mg capsule batch no.: 012114	113.91 ±31.54	127.23 ±33.66	54.94 ±19.48	1.10 ±0.55	0.3287 ±0.0881	10.73 ± 4.26	2.30 ±0.81

λ<sub>z</sub> = elimination rate constant; AUC<sub>%extrapol</sub> = percentage of the residual area extrapolated to time infinity in relation to the total area under the curve; AUC<sub>(0-∞)</sub> = Area Under the Curve, extrapolated to infinity; AUC<sub>(0-t)</sub> = Area Under the Curve, calculated from time zero until the last time point with quantifiable analyte concentrations; C<sub>max</sub> = Maximum Concentration; n = number of volunteers; R = reference, s.d. = standard deviation; T = test; t<sub>1/2</sub> = Terminal elimination half-life; t<sub>max</sub> = Time to reach maximum concentration

(reference preparation R1, dexketoprofen) resp. Muscoril 8 mg capsule (reference preparation R2, thiocolchicoside) is well comparable for AUC<sub>0-t</sub> of dexketoprofen, for AUC<sub>0-t</sub> of 3-O-glucuronide of thiocolchicoside (aglycone) and also for C<sub>max</sub> of 3-O-glucuronide of thiocolchicoside (aglycone) in 24 healthy male Caucasian subjects after single dose administration under fasting conditions. For C<sub>max</sub> of dexketoprofen the relative bioavailability of the test preparation shows increased values for geometric mean ratio and arithmetic mean ratio, however the 80–125 % acceptance range commonly used in bioequivalence trials is still met.

A clinically relevant difference in the tolerability and safety of the treatments was not detected.

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