sciendo

SJCAPP

Scandinavian Journal of Child and Adolescent Psychiatry and Psychology
Vol. 11:132-142 (2023) DOI 10.2478/sjcapp-2023-0014

Research Article **Open Access**

Pharmacokinetics of a Modified-Release Dexamphetamine Sulfate Formulation Following Single and Multiple Dosing in Healthy Adults: Comparative Bioavailability with Immediate-Release Dexamphetamine Sulfate, between Strengths, Assessment of Food and Meal Composition Effects

Henrik Uebel-von Sandersleben[1]*, Anke Mayer[2], Michaela Ruhmann[2], Oliver Dangel[2], Helmut Schütz[3,4]

[1]Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany
[2]Medical Department, MEDICE Arzneimittel Pütter GmbH & Co. KG, Iserlohn, Germany
[3]BEBAC – Consultancy Services for Bioequivalence and Bioavailability Studies, Vienna, Austria
[4]Center for Medical Data Science of the Medical University of Vienna, Vienna, Austria

***Corresponding author:** huebel@gwdg.de

Abstract

Background: A modified-release dexamphetamine sulfate formulation (DEX-MR) is under development for the treatment of attention-deficit/hyperactivity disorder.
Objective: We investigated the bioequivalence of once-daily DEX-MR to twice-daily immediate-release dexamphetamine sulfate (DEX-IR) after single and multiple dosing and between strengths, and effects of food and meal types.
Method: Three randomized, open-label, crossover studies in healthy males were conducted. In the single-dose study, participants received DEX-MR 20 mg, DEX-MR 10 mg (20 mg dose), and twice-daily DEX-IR 10 mg under fasted conditions and after a high-fat, high-calorie breakfast. In the breakfast study, participants received DEX-MR 20 mg and twice-daily DEX-IR 10 mg after a normocaloric and a high-fat, high-calorie breakfast. In the multiple-dose study, participants received DEX-MR 20 mg and twice-daily DEX-IR 10 mg for seven days each. In the run-in period (five days), participants consumed a normocaloric breakfast; on profile days, participants consumed a normocaloric breakfast (day 6) or a high-fat, high-calorie breakfast (day 7).
Results: Once-daily DEX-MR at a dose of 20 mg was bioequivalent to twice-daily DEX-IR 10 mg after single dosing under fasted and fed conditions and after multiple dosing under fed conditions. DEX-MR 10 mg and DEX-MR 20 mg were bioequivalent when administered as a single 20 mg dose. Food slightly reduced the rate and extent of absorption of DEX-MR and delayed the time to peak plasma concentration (t_{max}) by approximately two hours compared to the fasted state. Bioavailability of DEX-MR was comparable under different meal conditions (normocaloric vs. high-fat, high-calorie breakfast) both after single and multiple dosing.
Conclusions: Bioequivalence of once-daily DEX-MR and twice-daily DEX-IR was established. 1×2 DEX-MR 10 mg was bioequivalent to 1×1 DEX-MR 20 mg. DEX-MR should be administered with/after a meal to achieve the targeted pharmacokinetic profile (delayed t_{max}). Bioavailability of DEX-MR is not affected by meal composition (i.e., fat and caloric content).

Keywords: ADHD, dexamphetamine, comparative bioavailability, pharmacokinetic study

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental conditions of childhood. The worldwide prevalence of ADHD in children and adolescents is estimated at 7.2% (1). ADHD is characterized by the core symptoms of inattention, hyperactivity, and impulsivity that interfere with social, academic or occupational functioning (2). Successful ADHD management requires a comprehensive multimodal treatment plan, and may include both psychosocial and pharmacological interventions, that is tailored to

the individual's unique needs and preferences (3–6). Psychostimulants, including methylphenidate (MPH) and amphetamines (AMP), are the mainstay of ADHD treatment.

Numerous stimulant formulations are currently marketed, including short- and long-acting formulations. Immediate-release (IR) formulations usually have a short half-life and duration of action and thus often require multiple daily dosing, which is associated with various challenges, including an increased risk of non-compliance, social stigma associated with dosing during school time, and potential for medication misuse/diversion (7). Therefore, once-daily formulations have been developed to eliminate the need for multiple daily dosing.

Currently marketed AMP products include IR and modified-release (MR) formulations containing different AMP salts and enantiomers (7). A tablet formulation of immediate-release dexamphetamine sulfate (Attentin®/Amfexa®/Tentin®, hereinafter referred to as DEX-IR) received market authorization in Germany in 2011 and is currently marketed in several countries. The product is available in strengths of 5 mg, 10 mg, and 20 mg. DEX-IR is indicated as part of a comprehensive treatment program for ADHD in children and adolescents aged 6 to 17 years when response to previous MPH treatment is considered clinically inadequate (8). The effectiveness and safety of DEX-IR in the routine treatment of children and adolescents with ADHD were shown in an observational study. Most participants administered DEX-IR once daily; however, a large proportion of participants (approx. 40%) required twice daily dosing, presumably to extend the duration of action to the late afternoon and evening (9).

Therefore, a novel once-daily MR formulation of dexamphetamine sulfate (DEX-MR) was developed with the aim of achieving a biphasic pharmacokinetic profile mimicking twice-daily dosing of DEX-IR. DEX-MR was formulated to provide an initial rapid release of dexamphetamine followed by a period of prolonged release, thereby combining a rapid onset with an extended duration of action. DEX-MR consists of a hard gelatin capsule containing two types of drug-loaded pellets in a 1:1 ratio: uncoated pellets immediately dissolving in the acidic milieu of the stomach, and enteric-coated pellets dissolving at a pH value above 5.5, i.e., when reaching the duodenum. The DEX-MR formulation was developed in the strengths of 5, 10, 15, and 20 mg to cover the dose range of 5 mg to 20 mg (up to 40 mg in rare cases), as currently approved for DEX-IR tablets, with a single intake of one or two capsules in the morning.

The clinical development program for DEX-MR included three phase I studies that investigated the pharmacokinetic characteristics of DEX-MR in healthy adults. These studies were designed in accordance with applicable regulatory guidelines, specifically the 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms' of the European Medicines Agency (EMA) (10). The main objective of the PK study program was to establish similar bioavailability between a single dose of DEX-MR given in the morning and the same total dose of DEX-IR split into two equal doses given in the morning and four hours later.

Methods

Study population

All three studies were conducted in South Africa. The studies enrolled healthy non-smoking males between 18 and 55 years of age, with a body weight of at least 50 kg and a body mass index of 18.5 to 30 kg/m^2. Female subjects were excluded to avoid risks to the unborn child in case of pregnancy. Participants were required to be healthy as determined by medical history (participant-reported), vital signs, physical examination, standard 12-lead electrocardiogram (ECG) and laboratory investigations. Participants agreed to comply with all study procedures and to use effective contraception during the study and for three months after receiving the last dose of study drug. A summary of exclusion criteria is given in the Supplementary Material. Exclusion criteria included concomitant monoamine oxidase inhibitor treatment within 14 days before and during the study; concomitant treatment with agents that acidify or alkalinize the urinary fluids; treatment with any known cytochrome P450 enzyme altering agents (e.g., barbiturates, phenothiazines, cimetidine) within 30 days before the study; and treatment with any prescription medication within 14 days or over-the-counter or herbal remedies within seven days before first study drug administration, except if this would not affect the outcome of the study in the opinion of the investigator. Participants were not permitted to ingest food and beverages containing grapefruit and/or pomelo for ten days before and during the study, food and beverages containing other citrus fruits and/or apple or pineapple for 72 hours before and during the study, food and beverages containing alcohol and/or methylxanthines, and poppy seeds for 48 hours before and during the study.

Study design

The study protocols, including subject information sheets and informed consent forms, were reviewed and approved by an independent ethics committee (Health Sciences Research Ethics Committee, Bloemfontein, South Africa) and by the South

African Health Products Regulatory Authority. Participants were recruited from a volunteer database via text message. Compensation of participants was reasonable and related to the nature and degree of inconvenience and discomfort expected to result from participation in the study. Subjects provided written informed consent before screening. All three studies were randomized, open-label, laboratory-blind, crossover studies in healthy males conducted at a single center. In all studies, participants were required to fast overnight for at least ten hours before dosing. The test product DEX-MR and the reference product DEX-IR were both administered at a total daily dose of 20 mg: DEX-MR was administered as a single 20 mg dose (i.e., one capsule of DEX-MR 20 mg or two capsules of DEX-MR 10 mg), whereas the reference product DEX-IR 10 mg was administered twice daily four hours apart. The capsules or tablets were swallowed whole with 240 mL of water. For fed treatment periods, participants consumed a meal within 30 minutes before dosing. Water was allowed as desired except for one hour before and one hour after drug administration. Participants fasted for at least five hours post-morning-dose and received a standardized lunch at 5:15 hours post-dose.

Single-dose study

The single-dose study was a six-sequence, six-period crossover study under fasted and fed conditions. The objectives of the single-dose study were 1) to compare bioavailabilities of a single 20 mg dose of DEX-MR (1 × 20 mg or 2 × 10 mg) with DEX-IR 10 mg b.i.d., 2) to compare the bioavailability of DEX-MR 10 mg with 20 mg, and 3) to investigate the influence of food on the bioavailability of DEX-MR. A further objective was to evaluate the safety and tolerability of the study drugs. Participants were randomized to one of six treatment sequences: a single dose of DEX-MR 20 mg, a single dose of DEX-MR 10 mg (2 × 10 mg), and two doses of DEX-IR 10 mg taken four hours apart were administered once under fasted and once under fed conditions. The treatment periods included a profile period of 72 h and were separated by washout periods of seven days. During the fed treatment periods, participants consumed a high-fat, high-calorie breakfast that contained 800–1000 kilocalories, consisting of carbohydrate (~250 kilocalories), protein (~150 kilocalories) and fat (500–600 kilocalories), as recommended for food effect studies (10). The breakfast consisted of an omelet with whole milk and butter/margarine, whole wheat white bread rolls, fried bacon with fat, fried potato croquette/chips, butter, tomatoes and fresh whole milk (see Supplementary Table S1 for the meal composition).

Breakfast study

This study was a four-sequence, four-period crossover study under fed conditions. The objective of the study was to investigate the effects of different meal types (normocaloric vs. high-fat, high-calorie breakfast) on the bioavailability of DEX-MR and DEX-IR. The safety and tolerability of the study drugs were also evaluated. Participants were randomized to one of four treatment sequences: a single dose of DEX-MR 20 mg and two doses of DEX-IR 10 mg taken four hours apart were administered once after consumption of a normocaloric breakfast and once after consumption of a high-fat, high-calorie breakfast. The treatment periods included a profile period of 72 h and were separated by washout periods of 7 to 14 days. The high-fat, high-calorie breakfast was identical to the one used in the single-dose study. The normocaloric breakfast contained 500–600 kilocalories, consisting of carbohydrate (45–65% of energy), protein (10–35% of energy) and fat (20–35% of energy), as per FDA recommendations. The breakfast consisted of muesli with nuts, low-fat milk and orange juice (see Supplementary Table S2 for the meal composition).

Multiple-dose study

This study was a multiple-dose, two-sequence, two-period crossover study under fed conditions. The main objective of the study was to compare bioavailabilities of DEX-MR 20 mg and DEX-IR 10 mg b.i.d. at steady-state under fed conditions. A further objective was to evaluate the safety and tolerability of the study drugs. Participants were randomized to one of two treatment sequences: a single dose of DEX-MR 20 mg followed by two doses of DEX-IR 10 mg taken four hours apart, or vice versa. To ensure that steady-state was reached, each treatment period consisted of a run-in period of five days followed by two profile periods of 24 hours each (days 6 and 7). Treatment periods were separated by a washout period of 7 to 14 days. According to the EMA's recommendations, normocaloric meals should be used throughout a multiple-dose PK study including profile days, if the summary of product characteristics (SmPC) recommends intake under fed conditions, unless different meal conditions are mandated in the SmPC (10). In line with this requirement, normocaloric meals were used in the run-in periods as well as on profile day 6. As it was not known at the time the multiple-dose study was initiated whether the type of breakfast (normocaloric vs. high-fat, high-calorie) would have any decisive impact on the bioavailability of DEX-MR or DEX-IR, a second profile day on which the high-fat, high-calorie breakfast was to be consumed was included. The normocaloric meal consisted of two boiled eggs, two Weet-Bix, rooibos

tea, sugar, and low-fat milk (see Supplementary Table S3 for the meal composition). The high-fat, high-calorie meal was identical to the one used in the single-dose and breakfast study.

Blood sampling, bioanalysis and pharmacokinetic assessments
In the single-dose study, blood samples (2 mL) for PK analysis were collected pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.33, 4.67, 5, 5.25, 5.5, 5.75, 6, 6.33, 6.67, 7, 7.33, 7.67, 8, 9, 16, 24, 48, 60, and 72 h post-dose. In the breakfast study, samples (4 mL) were collected pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 12, 24, 36, 48, and 72 h post-dose. In the multiple-dose study, pre-dose samples (4 mL) were collected on days 4 to 7 to assess steady-state achievement by day 6. On days 6 and 7, samples (4 mL) were collected at 0.5, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, and 24 h post-dose. An indwelling venous cannula was inserted before dosing on profile days. Blood draws during the run-in period of the multiple-dose study were performed using a syringe and needle.
Blood samples were collected into dipotassium ethylenediaminetetraacetic acid (K_2EDTA) plastic tubes. Plasma was separated by centrifugation at 4 °C and stored at -20 °C until analysis. Plasma concentrations of dexamphetamine were measured at FARMOVS Bioanalytical Services Division (Bloemfontein, South Africa) using a validated liquid chromatography with a tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) of dexamphetamine was 0.469 ng/mL and the calibration range was 0.469 to 120 ng/mL. Samples were analyzed on a Sciex API4000QTRAP / API4000 using Watson Analyst® (version 1.6.2 / 1.6.3) and LIMS™ (version 7.4.2) software. The within-run (im)precision ranged from 0.6% to 2.1% and the within-run (in)accuracy ranged from -1.9% to 6.0%. The between-run (im)precision ranged from 1.2% to 1.6% and the between-run (in)accuracy ranged from -0.9% to 5.0%.

Pharmacokinetic analyses
Concentrations below the LLOQ prior to time to maximum observed plasma concentration (t_{max}) were set to zero. The area under the plasma concentration vs. time curve (AUC) was calculated using the linear-up/logarithmic-down trapezoidal method.
In the single-dose and breakfast study, PK metrics included the maximum observed plasma concentration (Cmax), AUC from time zero to the time of the last quantifiable concentration (AUC_{0-t}), AUC with extrapolation to infinity ($AUC_{0-\infty}$), t_{max}, and the apparent elimination half life ($t_{½}$).
In the multiple-dose study, PK metrics included the maximum observed concentration at steady-state ($C_{max,ss}$), the concentration at the end of the dosing interval τ ($C_{\tau,ss}$), AUC during the dosing interval ($AUC_{0-\tau,ss}$), time to maximum plasma concentration ($t_{max,ss}$), the minimum plasma concentration ($C_{min,ss}$), the average plasma concentration ($C_{av,ss}$) calculated as $AUC_{0-\tau,ss/\tau}$, and fluctuation $(C_{max,ss} - C_{min,ss})/C_{av,ss}$.

Safety assessments
In all studies, assessments of safety and tolerability included monitoring of adverse events (AEs), vital sign measurements, physical examinations, ECGs, and laboratory investigations (hematology, clinical chemistry and urinalysis). Prior and concomitant medications were also recorded. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0.

Statistical analyses
PK metrics were calculated for each participant and treatment using non-compartmental analysis based on the actual sampling time points. Statistical analyses were performed using Phoenix® WinNonlin® version 8.3.4. A mixed effects model was fitted to the $\log_e$-transformed values of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ in the single-dose and breakfast studies, and of Cmax,ss, Cτ,ss and $AUC_{0-\tau,ss}$ in the multiple-dose study. Treatment, period, and sequence were included as fixed effects in the model and subject within sequence as a random effect. The estimated geometric least squares means ratios and their associated 90% confidence intervals (CIs) of the $\log_e$-transformed data were back-transformed. In accordance with regulatory requirements (10), bioequivalence or lacking food effects were concluded if the 90% CI was entirely contained within the range 80.00% to 125.00% for AUC_{0-t}, $AUC_{0-\infty}$ and Cm$_{ax}$ (single-dose and breakfast studies) and for $C_{max,ss}$, $C_{\tau,ss}$ and $AUC_{0-\tau,ss}$ (multiple-dose study), respectively. In the single-dose studies evaluation was performed according to the 'Two at a Time' approach (11–14), i.e., treatments not relevant in the pairwise comparison were excluded from the data set whilst the codes for period and sequence were kept. No adjustments were made for multiple comparisons (15).

Results
Study population
In the single-dose study, 28 of 30 participants completed the study. One participant withdrew consent after treatment period 1 due to personal reasons. One participant was withdrawn upon admission to treatment period 2 due to a positive cotinine test. In the breakfast study, 19 of 20 participants completed the study. One participant was withdrawn prior to treatment period 4 due to numerous AEs. In the multiple-dose study, 46 of 50

participants completed the study. Four participants were withdrawn by the investigator; two for violating the protocol and two for safety reasons. Demographic and baseline characteristics of the study populations were comparable across the studies. Mean age ranged from 29.7 to 30.3 years; most participants were black (Supplementary Table S4).

Single-dose study

Sampling was sufficiently long to obtain reliable estimates of AUC_{0-t}: Extrapolated AUC was 1.06% (median; range 0.26–3.76%). Plasma concentration-time profiles for dexamphetamine following single-dose administration of DEX-MR and DEX-IR under fasted and fed conditions are shown in Figure. 1. PK metrics are summarized in Supplementary Table S5 and comparative bioavailability analyses are shown in Table 1.

Under both fasted and fed conditions, the PK profile of the reference treatment DEX-IR had an early peak (at 1.75 h and 1.5 h, respectively) and a second, higher peak at around six hours, which is consistent with the b.i.d. dosing regimen. In contrast, the administration of DEX-MR resulted in a PK profile with a ~4–6 hour plateau phase during which concentrations do not drop below 75% of the peak plasma concentration. Similar profiles were observed in the other studies (Figures 2 and 3). The mean C_{max} for DEX-MR 10 mg and DEX-MR 20 mg was slightly lower than that of the reference treatment. DEX-MR 10 mg and DEX-MR 20 mg had similar PK profiles over time. The mean $t_{½}$ of DEX-MR ranged from 10.50 to 10.93 h and was comparable to DEX-IR with 10.68 to 10.92 h.

TABLE 1. Comparative bioavailabilities of DEX-MR (20 mg dose) and DEX-IR 10 mg b.i.d. under fasted and fed conditions (single-dose study), 28 subjects.

PK metric (unit)	Geometric Least Squares Mean		PE (%)	90% CI	CV_{intra} (%)	CV_{inter} (%)
		Fasted conditions				
	DEX-MR 10 mg 1×2	DEX-IR 10 mg b.i.d.				
C_{max} (ng/mL)	53.94	57.82	93.29	91.26 – 95.36	4.78	12.40
AUC_{0-t} (h×ng/mL)	914.8	884.4	103.43	99.81 – 107.18	7.75	15.11
$AUC_{0-\infty}$ (h×ng/mL)	926.2	895.6	103.41	99.66 – 107.30	8.03	15.39
	DEX-MR 20 mg 1×1	DEX-IR 10 mg b.i.d.				
C_{max} (ng/mL)	53.98	57.82	93.35	90.71 – 96.08	6.24	10.25
AUC_{0-t} (h×ng/mL)	871.8	884.4	98.57	95.91 – 101.31	5.94	16.16
$AUC_{0-\infty}$ (h×ng/mL)	882.0	895.6	98.48	95.77 – 101.27	6.06	16.66
	DEX-MR 10 mg 1×2	DEX-MR 20 mg 1×1				
C_{max} (ng/mL)	53.94	53.97	99.95	97.15 – 102.82	6.18	11.26
AUC_{0-t} (h×ng/mL)	914.3	872.2	104.82	101.94 – 107.79	6.09	15.22
$AUC_{0-\infty}$ (h×ng/mL)	925.7	882.5	104.90	101.91 – 107.98	6.31	15.51
		Fed conditions				
	DEX-MR 10 mg 1×2	DEX-IR 10 mg b.i.d.				
C_{max} (ng/mL)	48.67	57.00	85.38	81.25 – 89.72	10.80	9.39
AUC_{0-t} (h×ng/mL)	816.6	821.2	99.44	96.20 – 102.80	7.21	13.89
$AUC_{0-\infty}$ (h×ng/mL)	825.5	831.5	99.28	95.98 – 102.70	7.35	14.02
	DEX-MR 20 mg 1×1	DEX-IR 10 mg b.i.d.				
C_{max} (ng/mL)	47.53	57.00	83.37	79.06 – 87.92	11.55	10.88
AUC_{0-t} (h×ng/mL)	817.8	821.2	99.59	96.44 – 102.84	6.97	11.04
$AUC_{0-\infty}$ (h×ng/mL)	828.7	831.5	99.66	96.44 – 103.00	7.14	11.01
	DEX-MR 10 mg 1×2	DEX-MR 20 mg 1×1				
C_{max} (ng/mL)	48.59	47.61	102.06	95.66 – 108.51	13.42	12.19
AUC_{0-t} (h×ng/mL)	816.0	818.4	99.71	95.84 – 103.73	8.63	12.11
$AUC_{0-\infty}$ (h×ng/mL)	824.9	829.3	99.47	95.48 – 103.62	8.93	12.07

AUC_{0-t}, area under the plasma concentration vs. time curve from time zero to the time of the last quantifiable concentration; $AUC_{0-\infty}$, area under the plasma concentration vs. time curve extrapolated to infinite time; C_{max}, maximum observed concentration; CI, confidence interval of point estimate; CV_{inter}, inter- (between-) subject coefficient of variation; CV_{intra}, intra- (within-) subject coefficient of variation; DEX-IR, immediate-release dexamphetamine sulfate; DEX-MR, modified-release dexamphetamine sulfate; PE, point estimate (ratio of geometric least squares means); PK, pharmacokinetic

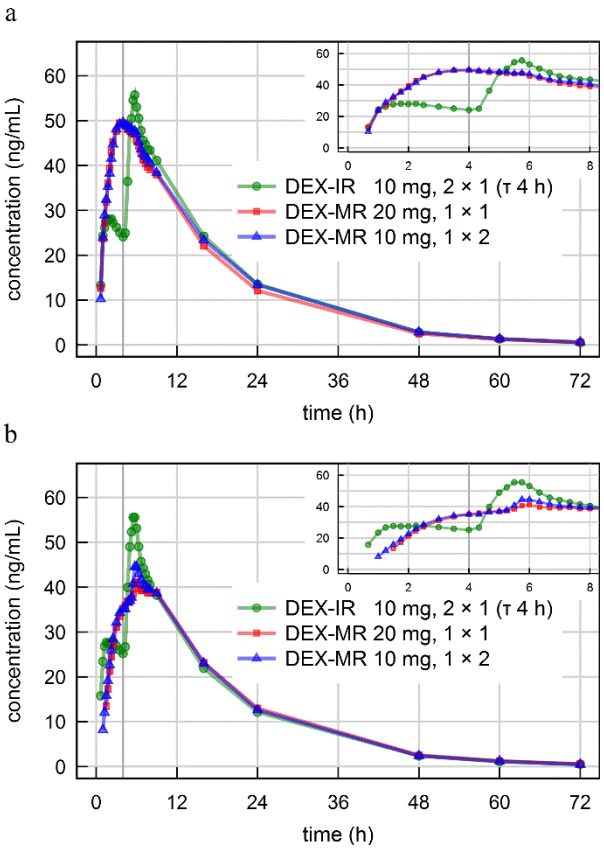

FIGURE 1. *Geometric mean dexamphetamine plasma concentration-time profiles following single-dose administration of DEX-MR and DEX-IR in (a) fasted and (b) fed state.*

Comparative Bioavailability of DEX-MR and DEX-IR

Under fasted conditions, a single 20 mg dose of DEX-MR 20 mg or DEX-MR 10 mg was bioequivalent to DEX-IR 10 mg given twice daily (τ 4 hours) with respect to rate (C_{max}) and extent ($AUC0_{-t}$ and $AUC_{0-\infty}$) of bioavailability, since the 90% CIs of these PK metrics lied well within the pre-defined acceptance range of 80.00% to 125.00%. Median t_{max} of DEX-MR was shorter compared to DEX-IR for both the 20 mg (3.50 h vs. 5.75 h) and 10 mg (4.00 h vs. 5.75 h) strengths.

Under fed conditions, DEX-MR 10 mg (20 mg dose) was bioequivalent to DEX-IR 10 mg given twice daily (τ 4 hours), both for rate and extent of bioavailability. DEX-MR 20 mg met the bioequivalence criteria for AUC_{0-t} and $AUC_{0-\infty}$. However, for C_{max}, with 79.06% the lower confidence limit was slightly below the lower boundary of the acceptance range. Median t_{max} of DEX-MR was similar to the one of DEX-IR for both the 20 mg (6.00 h vs. 5.63 h) and 10 mg (6.00 h vs. 5.63 h) strengths.

Under fasted conditions intra-subject variability of all PK metrics was low (4.78–8.03%) and inter-subject variability moderate (10.25–16.66%). Under fed conditions intra-subject variability was slightly higher (6.97–11.55%) and inter-subject variability slightly lower (9.39–14.02%).

Comparative Bioavailability of the 10 mg and 20 mg strengths of DEX-MR

DEX-MR 10 mg and DEX-MR 20 mg, when administered as a single 20 mg dose, showed comparable bioavailability under both fasted and fed conditions. The 90% CIs of the geometric least squares ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were entirely within the pre-defined bioequivalence acceptance range of 80.00% to 125.00%.

Food effect (exploratory analysis)

Both DEX-MR 10 mg and DEX-MR 20 mg showed comparable bioavailability when administered under fasted compared to fed conditions (Table 2). Under fasted conditions a relevant dose dumping was not

TABLE 2. PK metrics and food effect assessment – DEX-MR 10 mg (20 mg dose) and DEX-MR 20 mg (single-dose study), 28 subjects.

PK metric (unit)	Geometric Least Squares Mean		PE (%)	90% CI	CV_{intra} (%)	CV_{inter} (%)
	DEX-MR 10 mg (1×2)					
	fasting	fed				
C_{max} (ng/mL)	53.94	48.67	110.83	105.56 – 116.26	10.39	11.35
AUC_{0-t} (h×ng/mL)	914.8	816.6	112.02	107.91 – 116.29	8.12	14.56
$AUC_{0-\infty}$ (h×ng/mL)	926.2	825.5	112.20	107.93 – 116.63	8.41	14.56
	DEX-MR 20 mg (1×1)					
	fasting	fed				
C_{max} (ng/mL)	53.98	47.53	113.58	107.45 – 120.05	12.06	10.23
AUC_{0-t} (h×ng/mL)	871.8	817.8	106.61	102.43 – 110.96	8.68	11.59
$AUC_{0-\infty}$ (h×ng/mL)	882.0	828.7	106.44	102.16 – 110.89	8.91	11.78

AUC_{0-t}, area under the plasma concentration vs. time curve from time zero to the time of the last quantifiable concentration; $AUC_{0-\infty}$. area under the plasma concentration vs. time curve extrapolated to infinite time; C_{max}, maximum observed concentration; CI, confidence interval of point estimate; CV_{inter}, inter- (between-) subject coefficient of variation; CV_{intra}, intra- (within-) subject coefficient of variation; DEX-IR, immediate-release dexamphetamine sulfate; DEX-MR, modified-release dexamphetamine sulfate; PE, point estimate (ratio of geometric least squares means); PK, pharmacokinetic

observed. Administration under fasted conditions increased C_{max} by ~12% and AUC_{0-t} by ~9% compared to administration after a high-fat meal. For both strengths of DEX-MR, the 90% CIs of the geometric least squares ratios (fasted/fed) for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were entirely within the bioequivalence acceptance range of 80.00% to 125.00%, indicating lacking food effects on the overall exposure to DEX-MR. However, food prolonged the median tmax from 4.00 to 5.75 h for DEX-MR 10 mg and from 3.50 to 6.00 h for DEX-MR 20 mg, indicating that food delays the absorption of DEX-MR. $t_{½}$ was comparable between fasted and fed state.

Breakfast study

Sampling was sufficiently long to obtain reliable estimates of AUC_{0-t}: Extrapolated AUC was 2.17% (median; range 0.82–11.24%). Mean plasma concentration-time profiles for dexamphetamine following administration of DEX-MR 20 mg and DEX-IR 10 mg b.i.d. under different breakfast conditions (normocaloric vs. high-fat, high-calorie) are shown in Figure 2. PK metrics are summarized in Supplementary Table S6 and comparative bioavailability analyses are shown in Table 3.

A slightly lower rate and extent of absorption (i.e., C_{max} and AUC) were observed for both DEX-MR and DEX-IR when consumed after a high-fat, high-calorie breakfast compared to a normocaloric breakfast. The bioavailability of DEX-MR was comparable to that of DEX-IR both when administered after consumption of a normocaloric and a high-fat, high-calorie breakfast. Like in the single-dose study, a slightly lower mean C_{max} was observed for DEX-MR compared to DEX-IR when given after a high-fat, high-calorie breakfast. A slightly reduced mean C_{max} was also observed under normocaloric breakfast conditions. The 90% CIs of the geometric means ratios for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were entirely within the pre-defined acceptance range of 80.00% to 125.00%, indicating lacking effects of the type of breakfast between the two formulations.

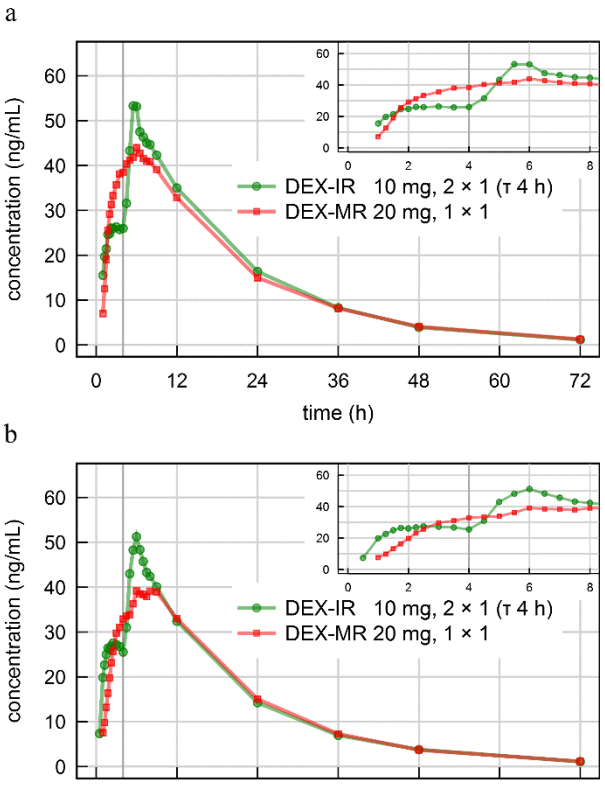

FIGURE 2 Geometric mean dexamphetamine plasma concentration-time profiles following administration of DEX-MR 20 mg and DEX-IR 10 mg b.i.d. after intake of a normocaloric (a) and a high-fat, high-calorie breakfast (b)

TABLE 3. Comparative bioavailabilities of DEX-MR 20 mg and DEX-IR 10 mg b.i.d. after intake of a normocaloric vs. a high-fat, high-calorie breakfast (breakfast study), 20 subjects.

PK metric (unit)	Geometric Least Squares Mean		PE (%)	90% CI	CV_{intra} (%)	CV_{inter} (%)
	Normocaloric breakfast					
	DEX-MR 20 mg	DEX-IR 10 mg b.i.d.				
C_{max} (ng/mL)	48.16	55.48	86.79	83.89 – 89.79	6.16	13.42
AUC_{0-t} (h×ng/mL)	955.8	989.5	96.60	92.98 – 100.36	6.93	18.12
$AUC_{0-\infty}$ (h×ng/mL)	982.5	1012.9	97.00	93.24 – 100.91	7.16	18.97
	High-fat, high-calorie breakfast					
	DEX-MR 20 mg	DEX-IR 10 mg b.i.d.				
C_{max} (ng/mL)	45.82	53.98	84.88	80.07 – 89.99	10.31	13.37
AUC_{0-t} (h×ng/mL)	908.3	914.7	99.31	95.47 – 103.31	6.93	17.09
$AUC_{0-\infty}$ (h×ng/mL)	932.4	942.5	98.93	95.31 – 102.68	6.54	17.08

AUC_{0-t}, area under the plasma concentration vs. time curve from time zero to the time of the last quantifiable concentration; $AUC_{0-\infty}$, area under the plasma concentration vs. time curve extrapolated to infinite time; C_{max}, maximum observed concentration; CI, confidence interval of point estimate; CV_{inter}, inter- (between-) subject coefficient of variation; CV_{intra}, intra- (within-) subject coefficient of variation; DEX-IR, immediate-release dexamphetamine sulfate; DEX-MR, modified-release dexamphetamine sulfate; PE, point estimate (ratio of geometric least squares means); PK, pharmacokinetic

Multiple-dose study

Plasma concentration-time profiles for dexamphetamine following DEX-MR 20 mg and DEX-IR 10 mg b.i.d. at steady-state are shown in Figure 3. PK metrics are summarized in Supplementary Table S7 and comparative bioavailability analyses are shown in Table 4.

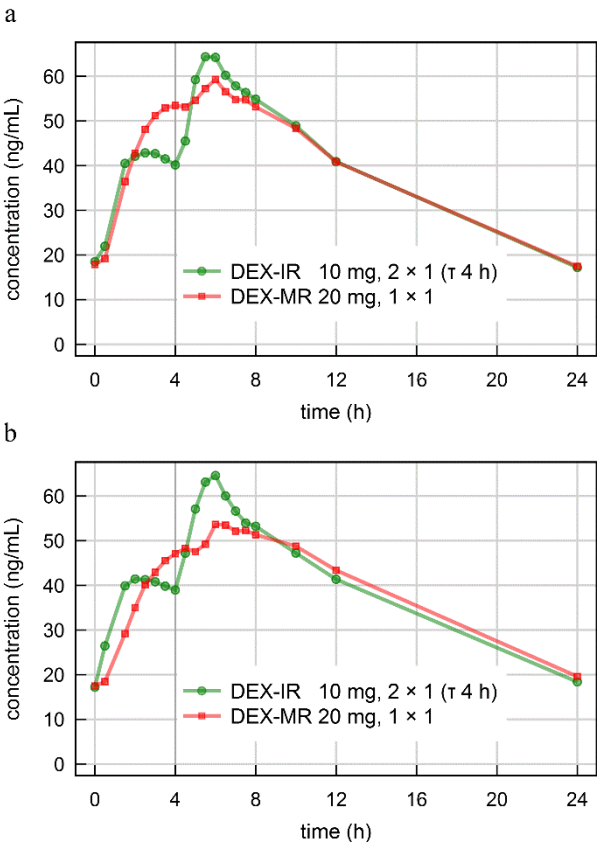

FIGURE 3. Geometric mean dexamphetamine plasma concentration-time profiles at steady-state following administration of DEX-MR 20 mg and DEX-IR 10 mg b.i.d. after intake of (a) a normocaloric breakfast on day 6 and (b) a high-fat, high-calorie breakfast on day 7.

The PK profile of DEX-MR showed a plateau phase of ~7–8 hours with mean plasma concentrations ≥75% of the mean C_{max}. Mean pre-dose plasma concentrations for day 4 to 7 showed that steady state was reached by day 6 both for DEX-MR and DEX-IR (data not shown). DEX-MR 20 mg and DEX-IR 10 mg b.i.d. showed comparable bioavailability under both breakfast conditions. When administered after a high-fat, high-calorie breakfast, the mean $C_{max,ss}$ was slightly lower (reduction of ~12%) for DEX-MR compared to DEX-IR. However, the 90% CIs of the geometric least squares means ratios of $C_{max,ss}$, $C_{min,ss}$ and $AUC_{0-\tau,ss}$ were within the pre-defined bioequivalence range for both breakfast conditions.

Safety

Drug-related AEs reported by at least two participants across all treatment groups in each study are summarized in Supplementary Table S8. No serious adverse events or AEs of severe intensity were reported in any of the studies. In the single-dose study, 98 AEs were reported by 25 of 30 participants; 53 AEs were judged as drug-related. All AEs were of mild intensity, except for two that were of moderate intensity (headache and syncope). In the breakfast study, 24 AEs were reported by 11 of 20 participants; 22 AEs were judged as drug-related. All AEs were of mild intensity. One participant was withdrawn from the study before treatment period 4 due to numerous AEs. In the multiple-dose study, 122 AEs were reported by 36 of 50 participants; 93 AEs were judged as drug-related. All drug-related AEs were of mild intensity, except for two events of insomnia and one event of urinary tract obstruction, which were of moderate intensity. Two participants were withdrawn from the study due to AEs, one for drug-related insomnia and one for non-drug-related cellulitis right knee.

TABLE 4. Comparative bioavailabilities of DEX-MR 20 mg and DEX-IR 10 mg b.i.d. after intake of a normocaloric breakfast and a high-fat, high-calorie breakfast (multiple-dose study), 46 subjects.

PK metric (unit)	Geometric Least Squares Mean		PE (%)	90% CI	CV_{intra} (%)	CV_{inter} (%)
	Normocaloric breakfast (day 6)					
	DEX-MR 20 mg	DEX-IR 10 mg b.i.d.				
$C_{max,ss}$ (ng/mL)	64.08	67.31	95.20	93.18 – 97.26	6.13	14.16
$C_{\tau,ss}$ (h×ng/mL)	17.45	17.19	101.49	97.92 – 105.18	10.23	22.05
$AUC_{0-\tau,ss}$ (h×ng/mL)	904.3	897.9	100.71	98.99 – 102.45	4.91	16.19
	High-fat, high-calorie breakfast (day 7)					
	DEX-MR 20 mg	DEX-IR 10 mg b.i.d.				
$C_{max,ss}$ (ng/mL)	59.60	68.00	87.64	85.50 – 89.85	7.09	13.73
$C_{\tau,ss}$ (h×ng/mL)	19.58	18.38	106.51	102.63– 110.53	10.62	21.36
$AUC_{0-\tau,ss}$ (h×ng/mL)	895.4	903.5	99.11	97.35 – 100.90	5.12	15.55

$AUC_{0-\tau,ss}$, area under the plasma concentration vs. time curve during the dosing interval (steady-state); $C_{max,ss}$, maximum observed concentration (steady-state); $C_{\tau,ss}$, concentration at the end of the dosing interval (steady-state); CI, confidence interval of point estimate; CV_{inter}, inter- (between-) subject coefficient of variation; CV_{intra}, intra- (within-) subject coefficient of variation; DEX-IR, immediate-release dexamphetamine sulfate; DEX-MR, modified-release dexamphetamine sulfate; PE, point estimate (ratio of geometric least squares means); PK, pharmacokinetic

No clinically significant findings were noted in physical examinations, laboratory evaluations and ECGs, except for one drug-related AE of mild QT prolongation. Small increases in blood pressure and pulse rate after drug administration were observed, which can be attributed to the pharmacological action of the drugs. Mild drug-related AEs related to blood pressure and pulse rate (blood pressure increased and tachycardia) were reported for three subjects.

Discussion

Overall, the results of the studies demonstrate bioequivalence of a single 20 mg dose of DEX-MR and two doses of DEX-IR 10 mg administered four hours apart in healthy adults. In the single-dose study, the lower limit of the 90% CIs (79.06%) for C_{max} of DEX-MR 20 mg was slightly below the lower limit of the acceptance range of 80.00% under fed conditions. Of note, a post-hoc assessment of the sample size showed that the study was underpowered to show bioequivalence for C_{max} under fed conditions. The slightly reduced C_{max} for DEX-MR compared to DEX-IR observed in all studies is not considered to be of clinical relevance. Thus, for individuals treated with twice-daily DEX-IR, DEX-MR represents a potential alternative treatment option. A once-daily DEX formulation is particularly important for children and adolescents with ADHD, as it eliminates the need for multiple dosing during the school day, which may be associated with embarrassment/stigma as well as an increased risk of non-compliance and diversion (7).

The study results show that DEX-MR provides an initial release of dexamphetamine shortly after administration followed by a phase of delayed release, with a plateau phase of several hours with mean plasma concentrations ≥75 % of the peak plasma concentration. This release pattern resembles that of a typical sustained-release formulation, which might be due to the fact that the enteric-coated pellets continuously 'trickle' from the stomach into the duodenum, resulting in a more sustained pattern of release (16). This release profile is expected to provide a rapid onset of action combined with a prolonged duration of action lasting up to the late afternoon and evening. A long-acting DEX formulation may be beneficial for a significant number of pediatric ADHD patients. An observational study found that approx. 40% of children and adolescents with ADHD currently administer DEX-IR twice daily, highlighting the need for sustained efficacy throughout the day in managing ADHD symptoms (9).

In the single-dose study, bioequivalence between DEX-MR 20 mg and DEX-MR 10 mg at a dose of 20 mg in terms of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ was demonstrated. Thus, it can be assumed that DEX-MR is dose proportional in the range of 5 mg to 20 mg. These results are in line with those of other studies that have shown dose-proportional pharmacokinetics for most amphetamine formulations (7,17).

Food intake causes physiological changes in the gastrointestinal tract, such as delayed gastric emptying, increased release of bile salts, and increased gastrointestinal motility, which can influence the bioavailability of a drug (18). In the single-dose study, DEX-MR showed comparable bioavailability when administered under fasted compared to fed conditions, and no dose dumping effect was observed in the fasted state. As expected for this type of MR formulation, the envisioned delayed release of dexamphetamine was observed only under fed conditions, i.e., t_{max} was delayed from four to six hours when DEX-MR was administered under fed compared to fasted conditions.

These findings support the administration of DEX-MR with or shortly after a meal to achieve the desired PK profile. The observed effect on t_{max} under fed conditions is expected based on the biopharmaceutic properties of DEX-MR. The formulations consists of a capsule filled with 50% uncoated pellets that immediately dissolve in the acidic milieu of the stomach and 50% enteric coated pellets that dissolve at a pH value above 5.5, i.e., when reaching the duodenum (see Supplementary Figure S1 and Figure S2 for dissolution profiles). Without concomitant intake of food, the transit time through the stomach is shortened (18), and the pellets are emptied into the duodenum earlier than in the fed state. The food effects observed in this study are consistent with those observed in previous studies of various extended-release AMP formulations. In healthy adults, a high-fat or high-fat, high-calorie meal had minimal effects on the rate and extent of absorption of dexamphetamine but delayed t_{max} by about 0.5 to 5 hours compared to administration in the fasted state (19–22).

The results of the breakfast study and the multiple-dose study show that the meal composition (i.e. fat and caloric content) does not affect the bioavailability of DEX-MR or the bioequivalence of DEX-MR and DEX-IR under fed conditions. These findings indicate that DEX-MR provides a consistent dexamphetamine exposure regardless of meal conditions and supports administration of DEX-MR without restrictions in regards to the content of meals, which provides dosing flexibility and may contribute to enhanced compliance.

Low intra-subject variability was observed for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ after single-dose administration of DEX-MR and for $C_{max,ss}$, $C_{\tau,ss}$, and $AUC_{0-\tau,ss}$ after multiple-dose administration, respectively. These

results suggest that DEX-MR provides a consistent dexamphetamine exposure during the 24-hour dosing interval, which may reduce the risk of fluctuation-associated adverse events and rebound effects.

In all three studies, DEX-MR was generally well tolerated and no serious AEs were reported. The observed AEs were in line with the known safety profile of stimulant medications, and no new safety concerns were identified.

The studies have some limitations. A limitation is that the single-dose study was slightly underpowered to demonstrate bioequivalence between DEX-MR and DEX-IR under fed conditions. The studies were conducted in South Africa in mostly black participants, which limits generalizability to other populations. Insufficient data are available on the effects of race and ethnicity on the PK of amphetamines. The available data indicate that the PK profiles of amphetamines are similar between black and Caucasian populations (17). Furthermore, all participants were male, which also limits generalizability. Generally, women show a higher exposure to amphetamine compared to men; however, exposure is similar after normalization by dose and weight (17). The study was conducted in healthy volunteers, thus generalizability to the clinical target population may be limited. Further studies should evaluate the PK of DEX-MR in pediatric populations.

Conclusions

DEX-MR provides a rapid initial release of dexamphetamine followed by a subsequent prolonged phase of drug delivery. Once-daily DEX-MR at a dose of 20 mg was bioequivalent to twice-daily DEX-IR 10 mg after single dosing under fasted and fed conditions and after multiple dosing under fed conditions. DEX-MR 10 mg and DEX-MR 20 mg were bioequivalent when administered as a single 20 mg dose. Food intake delayed t_{max} by approximately two hours compared to the fasted state, supporting the administration of DEX-MR with or after a meal to achieve the targeted PK profile. No restrictions regarding the meal contents are necessary, as the meal composition (fat and caloric content) does not affect the bioavailability of DEX-MR.

Clinical Significance

The novel DEX-MR formulation is a potential alternative treatment option for individuals treated with twice-daily DEX-IR. The once-daily administration may offer benefits such as improved treatment adherence and reduced risk of misuse and diversion.

Acknowledgements

The studies were funded by MEDICE Arzneimittel Pütter GmbH & Co. KG.

Conflict of Interest

HU received speaker's fees from MEDICE Arzneimittel Pütter GmbH & Co. KG. AM, MR, and OD are full-time employees of MEDICE Arzneimittel Pütter GmbH & Co. KG. HS is a consultant; clients include private companies, associations of pharmaceutical manufacturers, and regulatory agencies.

References

1. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. Pediatrics. 2015;135(4):e994–1001.

2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Washington, DC. 5th ed. 2013.

3. National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: diagnosis and management [NICE guideline NG87]. 2018. https://www.nice.org.uk/guidance/ng87 Accessed 10 June 2022.

4. Wolraich ML, Hagan JF, Allan C, Chan E, Davison D, Earls M, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4):e20192528.

5. CADDRA – Canadian ADHD Resource Alliance: Canadian ADHD Practice Guidelines, 4.1 Edition, Toronto ON; CADDRA, 2020.

6. Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie Psychosomatik und Psychotherapie (DGKJP), Deutsche Gesellschaft für Psychiatrie und Psychotherapie Psychosomatik und Nervenheilkunde (DGPPN), & Deutsche Gesellschaft für Sozialpädiatrie und Jugendmedizin (DGPSJ). (Hrsg). (2018). Langfassung der interdisziplinären evidenz- und konsensbasierten (S3) Leitlinie „Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) im Kindes-, Jugend- und Erwachsenenalter". AWMF-Registernummer 028-045. https://www.awmf.org/uploads/tx_szleitlinien/028-045l_S3_ADHS_2018-06.pdf Accessed 13 June 2022.

7. Childress AC, Komolova M, Sallee FR. An update on the pharmacokinetic considerations in the treatment of ADHD with long-acting methylphenidate and amphetamine formulations. Expert Opin Drug Metab Toxicol. 2019;15(11):937–74.

8. MEDICE Arzneimittel Pütter GmbH & Co KG. Attentin 5/10/20 mg SmPC. 06/2020.

9. Uebel-von Sandersleben H, Dangel O, Fischer R, Ruhmann M, Huss M. Effectiveness and safety of dexamphetamine sulfate (Attentin®) in the routine treatment of children and adolescents with ADHD: results from a 12-month non-interventional study. Scand J Child Adolesc Psychiatr Psychol. 2021;9:73–86.

10. European Medicines Agency. EMA/CHMP/EWP/280/96 Rev1. Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms. 2014. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmacokinetic-clinical-evaluation-modified-release-dosage-forms_en.pdf Accessed 13 June 2022

11. European Medicines Agency. CPMP/EWP/QWP/1401/98 Rev.1/Corr** Guideline on the Investigation of Bioequivalence. London. 20 January 2010.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf Accessed 13 June 2022.

12. European Generic Medicines Association. Revised EMA Bioequivalence Guideline. Questions & Answers. London. June 2010. https://www.medicinesforeurope.com/wp-content/uploads/2016/03/EGA_BEQ_QA_WEB_QA_1_32.pdf Accessed 13 June 2022.

13. Schuirmann DJ. Two at a Time? Or All at Once? International Biometric Society, Eastern North American Region, Spring Meeting. Pittsburgh, PA. March 28–31, 2004.

14. D'Angelo P. Testing for Bioequivalence in Higher–Order Crossover Designs: Two-at-a-Time Principle Versus Pooled ANOVA. 2nd Conference of the Global Bioequivalence Harmonisation Initiative. Rockville, MD. 15–16 September, 2016.

15. Berger RL, Hsu JC. Bioequivalence Trials, Intersection-Union Tests and Equivalence Confidence Sets. Stat Sci. 1996;11(4):283–302.

16. Watanalumlerd P, Christensen JM, Ayres JW. Pharmacokinetic modeling and simulation of gastrointestinal transit effects on plasma concentrations of drugs from mixed immediate-release and enteric-coated pellet formulations. Pharm Dev Technol. 2007;12(2):193–202.

17. Markowitz JS, Patrick KS. The Clinical Pharmacokinetics of Amphetamines Utilized in the Treatment of Attention-Deficit/Hyperactivity Disorder. J Child Adolesc Psychopharmacol. 2017;27(8):678–89.

18. Koziolek M, Alcaro S, Augustijns P, Basit AW, Grimm M, Hens B, et al. The mechanisms of pharmacokinetic food-drug interactions – A perspective from the UNGAP group. Eur J Pharm Sci. 2019;134:31–59.

19. Tulloch SJ, Zhang Y, McLean A, Wolf KN. SLI381 (Adderall XR), a two-component, extended-release formulation of mixed amphetamine salts: bioavailability of three test formulations and comparison of fasted, fed, and sprinkled administration. Pharmacotherapy. 2002;22(11):1405–15.

20. Stark JG, Engelking D, McMahen R, Sikes C. A randomized crossover study to assess the pharmacokinetics of a novel amphetamine extended-release orally disintegrating tablet in healthy adults. Postgrad Med. 2016;128(7):648–55.

21. Krishnan S, Zhang Y. Relative bioavailability of lisdexamfetamine 70-mg capsules in fasted and fed healthy adult volunteers and in solution: a single-dose, crossover pharmacokinetic study. J Clin Pharmacol. 2008;48(3):293–302.

22. Wang Y, Yu M, Yan B, Martin P, Robertson B. Effects of Food on the Bioavailability of Amphetamine in Healthy Adults After Administration of SHP465 Mixed Amphetamine Salts Extended-Release Capsules. Drugs R D. 2019;19(2):167–75.