Formulation-dependent food effects demonstrated for nifedipine modified-release preparations marketed in the European Union

Barbara S. Schug[a,*], Erich Brendel[b], Dörte Wolf[a], Meinolf Wonnemann[a], Manfred Wargenau[c], Henning H. Blume[a]

[a]SocraTec R&D, Feldbergstr. 59, D-61440 Oberursel, Germany
[b]Bayer AG, Institute of Clinical Pharmacology, Aprather Weg, D-42096 Wuppertal, Germany
[c]M.A.R.C.O., Institute for Biomedical Statistics, Markenstr. 5–13, D-40227 Düsseldorf, Germany

Abstract

The objective of this study was a comparative investigation of the influence of concomitant food intake on the bioavailability of two nifedipine-containing controlled-release formulations. Adalat® OROS and CORAL® were compared in a randomised, non-blind, four-way crossover design in 24 healthy, male subjects after single dose administration following a high fat American breakfast or an overnight fast of 12 h, respectively. Plasma samples were withdrawn until 48 h post-dose. In the fasted state, the bioavailability (AUC and C_{max} values) was lower for CORAL® than for Adalat® OROS. Under fed conditions, differences in bioavailability between both products were markedly increased. With respect to the therapeutic use of both products, the most important finding was the significant dose-dumping effect observed after fed administration of CORAL®, resulting in nifedipine plasma concentrations of nearly three- to four-fold in 11 of 24 volunteers. The mean ratio of C_{max} was 235% comparing CORAL® with Adalat® OROS under these conditions. The formulation-dependent food interaction observed in this study may be therapeutically relevant, especially in the case of changing administration conditions or switching from one product to the other. © 2002 Published by Elsevier Science B.V.

1. Introduction

Modified release dosage forms are normally developed in order to reduce the dosing frequency for better therapeutic compliance in chronic treatment and/or to reduce maximum peak plasma levels in the case of concentration-related side-effects. On the other hand, such products bear the risk of formulation-related interactions during the absorption process, especially in the case of concomitant food intake (Blume et al., 1996). Furthermore, food effects are normally not predictable from the in-vitro characterisation of dosage forms, although a higher probability is observed for formulations with pH-dependent release properties. The general conclusion from numerous previous investigations is that food effects not only depend on the physicochemical properties of the drug, but often result from formulation characteristics (Karim et al., 1985a,b; Waldman and Morganroth, 1995). This is why current international regulatory guidelines request food interaction studies for the approval of newly developed modified release products as well as for generic developments (CPMP Note for Guidance, 1999; FDA, 1997).

Osmotically driven gastrointestinal therapeutic systems (GITS) were identified as being very robust towards potential food interactions (Modi et al., 2000). Such a system was developed for nifedipine (Adalat® OROS) in order to allow once-daily administration instead of the twice-daily dosage regimen required with conventional modified release tablets.

Nifedipine is a dihydropyridine with a molecular weight of 346.3 and a pK_a value of >13, and is practically insoluble in water. Such physicochemical properties of a drug may complicate the development of modified release dosage forms. However, other modified release nifedipine formulations for once-daily administration based on diverging galenic principles have been approved as generic

*Corresponding author. Tel.: +49-6171-5857-11; fax: +49-6171-5857-25.
E-mail address: barbara.schug@socratec-pharma.de (B.S. Schug).

forms by health authorities in the European Union. For one of these products, Slofedipine XL, a pronounced food interaction was detected, which resulted in significant lag-times with absorption-free time spans of more than 15 h in the majority of volunteers after fed administration (Schug et al., 2001). This investigation showed that, despite the harmonised registration requirements in the European Union, quality differences with a potential impact on efficacy and safety still exist.

The aim of this study was to compare the bio-availabilities of two 60 mg oral nifedipine modified release formulations, CORAL® (D.R. Drug Research S.R.L., Milano, Italy), a generic erosive tablet for once-daily administration, and Adalat® OROS (Bayer AG, Lever-kusen, Germany), both marketed in member states of the European Union, and to investigate the impact of concomi-tant food intake on the in-vivo performance of both products.

2. Methods

2.1. Clinical study

The study was performed in accordance with ICH-GCP requirements and the current version of the Declaration of Helsinki.

The investigations followed a randomised, non-blind, four-period changeover design in 24 healthy, male subjects with washout periods of at least 1 week between the treatment periods.

Pre-examination of the subjects included assessment of general health status by anamnesis and a physical examina-tion, blood pressure and pulse rate measurements, a 12-lead ECG, haematological and clinical chemical parame-ters as well as urinalysis. Inclusion and exclusion criteria were chosen to ensure the safety of the volunteers and to exclude pathological factors which might have an influence on the bioavailability of the products. Alcohol and drug tests were performed prior to each dosing.

Volunteers were hospitalised for 12 h prior to and for 48 h after dosing. Every subject received single oral doses of CORAL® (test) or of Adalat® OROS (reference) given under standardised conditions together with 150 ml non-carbonated water either after an overnight fast of at least 12 h and immediately after eating a high-fat breakfast.

The subjects remained in the supine position for another 4 h. Standardised meals were served 4, 7 and 11 h post-dose. Conditions were chosen in accordance with international requirements for food interaction studies (Draft Guidance for Industry, FDA, 1997). Blood samples for the analysis of nifedipine concentrations were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36 and 48 h after administration. Plasma was prepared under protection from daylight due to the photo-instability of nifedipine, deep frozen and stored below −20 °C until

analysis. For safety evaluation, vital signs, ECG and laboratory parameters were repeatedly determined during the hospitalisation phase. Subjective well-being was sur-veyed by actively requesting for adverse events in a non-leading manner and by documentation of spontaneous reporting. Adverse events as reported by the volunteers were classified according to severity and potential relation to the study medication. Any concomitant medication within the course of the study was documented.

Only healthy male, Caucasian subjects who had given their written consent were enrolled in the study. A total of 27 subjects entered the study. All 27 subjects included in the study were investigated for safety analysis. The mean age of the 27 subjects was 28.0 years (range 19–39 years), mean weight 78.3 kg (range 61–100 kg) and mean height 181.9 cm (range 167–202 cm). Average BMI was calcu-lated as 23.61 kg/m^2 (range 19.5–26.9 kg/m^2). Three of the subjects dropped out and were replaced: one subject dropped out from the study during the first period and refused any post-study examination for personal reasons; another volunteer withdrew due to severe headache and in the third case the volunteer was withdrawn after an adverse event had occurred which was classified as not related to the study medication. Thus, a total of 24 subjects com-pleted all four treatment periods of the study and were used for pharmacokinetic analysis.

2.2. In vitro dissolution

The investigational products, each containing 60 mg nifedipine, were tested prior to the clinical study with identical dissolution conditions in order to allow com-parability. After method optimisation, dissolution was performed with a standardised compendial Paddle ap-paratus with a rotation speed of 50 rpm ($n=6$ for each value) using different aqueous buffers containing 1% sodium dodecyl sulfate (SDS) in order to achieve sink conditions (0.1 N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8 and phosphate buffer pH 8.0, 900 ml each). All investigations were performed under complete protec-tion from daylight.

2.3. Bioanalytical procedure

Plasma samples were assayed using a LC–MS/MS method operating in the ESI (+) mode with MRM validated according to international requirements (Shah et al., 1992). Amlodipine was used as internal standard. The calibration curve obtained after linear regression ranged from 0.1 to 100.16 µg/l.

Quality control (QC) samples were analysed together with the study samples. Mean day-to-day precision values of the assay procedure as calculated from QC results were 7.69% (0.13 µg/l), 5.51% (6.43 µg/l) and 4.80% (79.09 µg/l). Accuracy was determined as a mean deviation of 0.27% (0.13 µg/l), −1.21% (6.43 µg/l), and −1.51%

(79.09 µg/l), respectively. All analyses were performed under total protection from daylight.

2.4. Pharmacokinetic evaluation

The pharmacokinetic parameters of nifedipine were determined model-independently for each subject by use of the WinNonlin software (version 3.0) considering the actual sampling times. All data analyses were performed with SAS$^{®}$ for Windows 95/NT (version 6.12, SAS Institute, Cary, NC, USA). C_{max} and t_{max} were read directly from the observed concentration–time points. Areas under the plasma concentration vs. time curves, AUC(0–t_n), were calculated according to the linear trapezoidal rule during the absorption phase and according to the logarithmic trapezoidal rule in the terminal phase until the time of the last quantifiable concentration. AUC(0–∞) was calculated as the sum of AUC(0–t_n) and AUC extrapolated from the last measured value to infinity considering the terminal elimination rate constant. Furthermore, AUC for the intended dosing interval of 24 h [AUC(0–24)] was also calculated. Lag-time, t_{lag}, was determined directly from the observed concentrations as the actual blood sampling time corresponding to the last sample with nifedipine concentrations below the LOQ after dosing and prior to the first quantifiable sample. Half-value duration (HVD) was calculated as the time that the plasma nifedipine concentration levels remained above 50% of the observed maximum concentration. Mean residence time (MRT), the average time a molecule remains in the body, was calculated as the ratio of AUMC-to-AUC(0–∞), where AUMC is the total area under the first moment curve from time zero to infinity.

The pharmacokinetic parameters AUC and C_{max} were assumed to be log-normally distributed. Log-transformed values of these pharmacokinetic characteristics were submitted to separate analyses of variance (ANOVA) considering sequence, subject (sequence), period, food, formulation, and food*formulation effects. Based on these analyses, point estimates for the ratio 'test/reference' following both fed and fasting conditions were calculated by re-transformation of the logarithmic data. The corresponding 95% confidence intervals were derived for further exploratory statistical assessment of differences using the within-subject variability from the ANOVA; occasionally, 90% confidence intervals were used for further investigation of the presence of a food interaction.

3. Results

Mean and individual plasma concentration vs. time profiles measured in this study are shown in Figs. 1–5, pharmacokinetic results are presented in Table 1 and the statistical evaluation is summarised in Table 2.

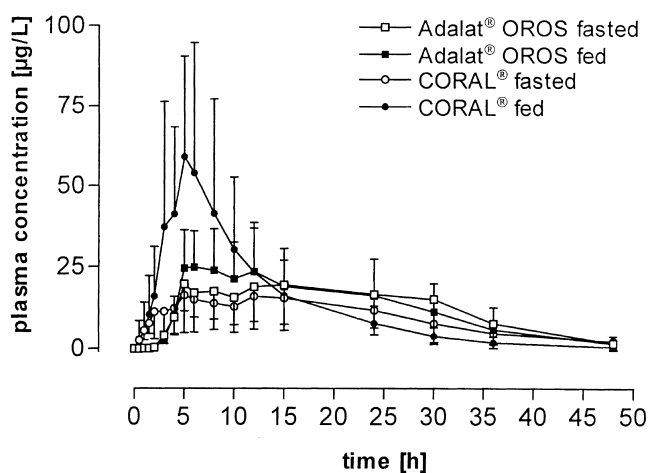The plasma concentration vs. time profiles of both

Fig. 1. Mean plasma concentration (±S.D.) vs. time curves of nifedipine determined after oral administration of Adalat$^{®}$ OROS and CORAL$^{®}$ under fasting conditions and after a high-fat breakfast in 24 healthy young volunteers in a four-period changeover design.

formulations determined after *fasted administration* showed a difference throughout the investigated 48 h blood sampling range (Fig. 1). After a lag time of 0.5 to 1.5 h (median 1 h), mean plasma concentrations of Adalat$^{®}$ OROS increased to a level of about 20 µg/l within the first 5 h, resulting in a plateau until nearly 24 h p.a., followed by a slow and continuous decrease until 48 h p.a. After administration of CORAL$^{®}$, the mean nifedipine profile increased without any lag time to a concentration of nearly 15 µg/l after 5 h, also followed by a plateau until about 24 h and a subsequent constant decrease of the curve.

The differences between the products after fasted administration as shown by the graphs were reflected in the major pharmacokinetic parameters and the statistical analysis. Mean AUC(0–∞) values of 395.9 µg h/l for CORAL$^{®}$ and 487.7 µg h/l for Adalat$^{®}$ OROS confirm a greater
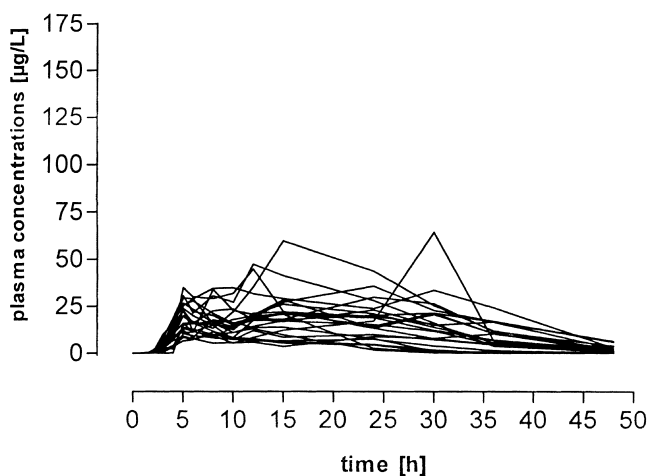

Fig. 2. Individual plasma concentration vs. time curves of nifedipine determined after oral administration of Adalat$^{®}$ OROS under fasting conditions in 24 healthy young volunteers in a four-period changeover design.
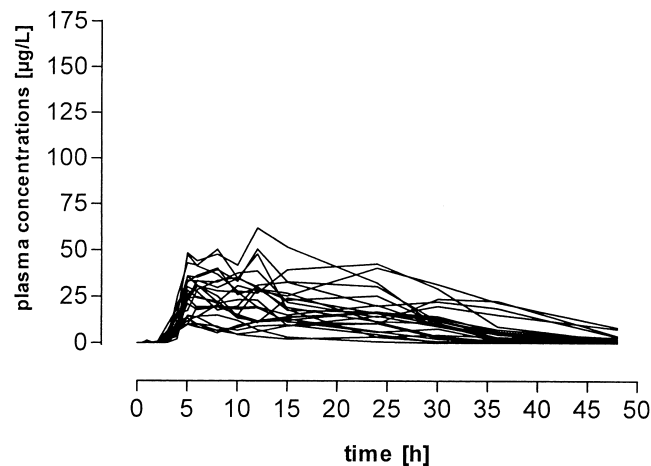
Fig. 3. Individual plasma concentration vs. time curves of nifedipine determined after oral administration of Adalat® OROS after a high-fat breakfast in 24 healthy young volunteers in a four-period changeover design.

Fig. 5. Individual plasma concentration vs. time curves of nifedipine determined after oral administration of CORAL® under fed conditions in 24 healthy young volunteers in a four-period changeover design.

nifedipine bioavailability for Adalat® OROS. AUC($0-t_n$) values were of a comparable magnitude to AUC($0-\infty$) since, in most cases, the extrapolated part of AUC($0-\infty$) was relatively small. For the intended dosage interval, AUC($0-24$) was calculated as only 272.8 µg h/l for CORAL®, whereas the corresponding value for Adalat® OROS was 321.4 µg h/l. C_{max} values (geometric mean) were 20.3 µg/l for CORAL® and 23.2 µg/l for Adalat® OROS. Since the shape of both profiles is similar, these differences clearly represent deviations in the extent of bioavailability and not in rate.

Statistical evaluation indicated lower values for C_{max} when comparing CORAL® with Adalat after fasted administration (point estimate: 87%, 95% CI: 74–103%), as well as for AUC($0-\infty$) (point estimate: 81%, 95% CI: 67–99%). Evaluation of AUC($0-24$) showed a similar result (point estimate: 85%, 95% CI: 72–100%).
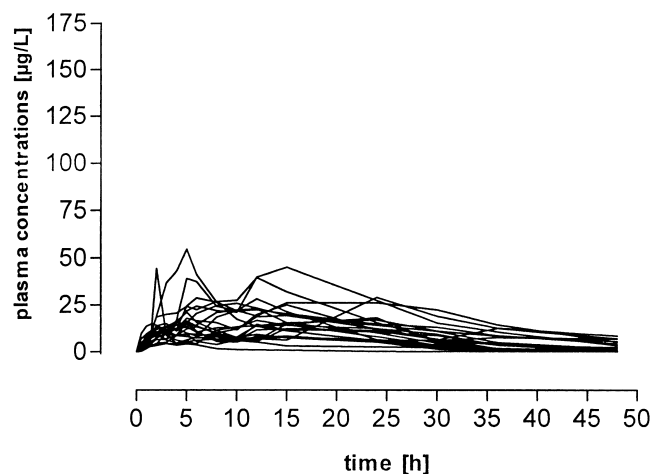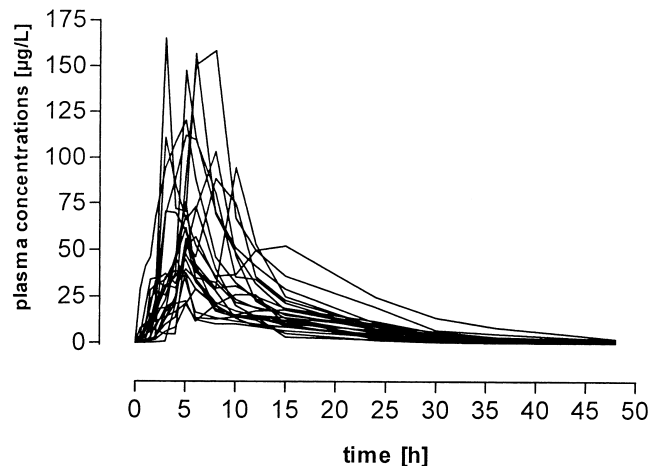

Fig. 4. Individual plasma concentration vs. time curves of nifedipine determined after oral administration of CORAL® under fasting conditions in 24 healthy young volunteers in a four-period changeover design.

Striking differences between the formulations were observed after administration under *fed conditions*. The mean plasma concentration vs. time curve of Adalat® OROS increased (after a lag time of 0.5 to 1.5 h) to slightly higher levels (about 24 µg/l) compared with fasting conditions, resulting in a plateau until nearly 24 h p.a. followed by a slow and continuous decrease until 48 h p.a. In contrast, the mean curve of CORAL® showed an enormous increase up to a maximum of about 55 µg/l after 5 h. This maximum was followed by a steep decrease until 15 h post-application. Mean plasma levels were clearly below those of Adalat® OROS beyond 15 h p.a.

Again, these differences in the shape of the curve were in accordance with the data obtained from pharmacokinetic evaluation. Total AUC($0-\infty$) (567.6 µgh/l for CORAL®, 502.4 µgh/l for Adalat® OROS) differed by approximately 10%, indicating a slightly higher extent of bioavailability after fed administration of CORAL®. Thus, the relation of the extent of bioavailability between the products is reversed when changing from fasted to fed administration. Extrapolated parts of AUC($0-\infty$) are small, thus no relevant differences are observed when comparing total AUC($0-\infty$) with AUC($0-t_n$). On the other hand, the difference between C_{max} values becomes striking under fed conditions: geometric means were calculated as 64.2 µg/l for CORAL® and 27.4 µg/l for Adalat® OROS. Under these conditions, the differences in C_{max} clearly reflect product-related discrepancies in drug release. Obviously, the release controlling system of CORAL® is switched off when co-administered with food.

In order to describe the specific modified release characteristics, MRT and HVD were calculated. MRT values were found to be comparable for both dosage forms under fasting conditions. Differences in the mean values of HVD reflect the course of the different profiles after administration of CORAL® compared with Adalat® OROS. The MRT and HVD values underline the assumption of a lack

Table 1
Geometric mean values/geometric S.D. (range) of nifedipine pharmacokinetic parameters in plasma following a single oral dose of 60 mg Adalat® OROS or 60 mg CORAL® in the fasted and fed state (all subjects valid for PK and safety, $N = 24$)

Parameter	Unit	Fasted state	Fed state
Adalat® OROS			
AUC(0–∞)[a]	μg h/l	487.7/1.88 (148.4–1172.1)	502.4/1.84 (135.4–1269.8)
AUC(0–t_n)	μg h/l	475.7/1.83 (147.7–1155.7)	495.4/1.81 (134.7–1155.74)
AUC(0–24)	μg h/l	321.3/1.68 (128.47–776.6)	357.3/1.75 (99.6–915.2)
AUC(t_n–∞)[a]	%	1.22/2.94 (0.22–11.05)	0.93/4.13 (0.14–14.2)
C_{max}	μg/l	23.2/1.63 (10.3–59.9)	27.4/1.61 (10.3–61.8)
$t_{1/2}$[a]	h	4.90/1.44 (2.58–9.69)	4.94/1.52 (2.32–12.9)
MRT[a]	h	19.1/1.25 (12.3–29.1)	17.9/1.30 (9.83–27.7)
HVD	h	21.2/1.49 (9.08–36.5)	17.3/1.58 (6.27–34.0)
t_{max}[b]	h	9 (5–36)	9 (5–30)
t_{lag}[b]	h	1 (0.5–1.5)	1.5 (0.5–3)
CORAL®			
AUC(0–∞)[a]	μg h/l	395.9/2.05 (43.0–1063.6)	567.6/1.65 (235.8–1359.2)
AUC(0–t_n)	μg h/l	376.8/1.95 (40.9–998.4)	562.8/1.65 (232.8–1339.2)
AUC(0–24)	μg h/l	272.7/1.82 (40.9–678.2)	506.9/1.66 (202.3–1192.5)
AUC(t_n–∞)[a]	%	1.90/3.70 (0.24–23.12)	0.59/2.35 (0.13–3.56)
C_{max}	μg/l	20.3/1.76 (5.58–54.5)	64.2/1.79 (21.0–165.0)
$t_{1/2}$[a]	h	6.36/1.63 (2.67–18.4)	5.63/1.31 (3.08–8.77)
MRT[a]	h	18.0/1.37 (8.09–35.6)	11.8/1.22 (7.61–17.27)
HVD	h	14.5/2.16 (0.96–31.3)	5.18/1.55 (2.20–17.6)
t_{max}[b]	h	8 (1–24)	5 (3–10)
t_{lag}[b]	h	0 (0–0)	0 (0–0.5)

[a] Only $N = 22$ observations available for the fasted state.
[b] Median (range).

of robustness of the generic formulation under fed conditions. MRT values of CORAL® showed a decrease from 18.0 h under fasted to 11.8 h under fed conditions, while HVD values were reduced from 14.5 to 5.18 h.

The within-product comparison of bioavailabilities after *fed vs. fasted* administration did not indicate a food effect in the case of Adalat® OROS. The mean fed vs. fasted AUC ratio was calculated as 106% (90% CI: 90–124%), which is within the generally used acceptance criteria for bioequivalence (80–125%). C_{max} was found to be slightly

Table 2
Statistical evaluation of the pharmacokinetic parameters for the comparison of Adalat® OROS and CORAL® under fasting conditions and after a high-fat breakfast with calculation of point estimates and affiliated confidence intervals

Parameter	Comparison	Mean ratio	95% CI
AUC(0–∞)	Fasted: CORAL®/Adalat® OROS	0.81	(0.67, 0.99)
	Fed: CORAL®/Adalat® OROS	1.11	(0.93, 1.33)
	Adalat® OROS: fed/fasted	1.06	(0.87, 1.28)
	CORAL®: fed/fasted	1.44	(1.20, 1.74)
AUC(0–24)	Fasted: CORAL®/Adalat® OROS	0.85	(0.72, 1.00)
	Fed: CORAL®/Adalat® OROS	1.42	(1.20, 1.68)
	Adalat® OROS: fed/fasted	1.11	(0.94, 1.32)
	CORAL®: fed/fasted	1.86	(1.57, 2.20)
C_{max}	Fasted: CORAL®/Adalat® OROS	0.87	(0.74, 1.03)
	Fed: CORAL®/Adalat® OROS	2.35	(2.00, 2.76)
	Adalat® OROS: fed/fasted	1.18	(1.00, 1.38)
	CORAL®: fed/fasted	3.17	(2.70, 3.72)

increased with food; the mean fed vs. fasted ratio was 118% (90% CI: 103–135%). The mean ratio for AUC(0–24) for this within-product comparison was calculated as 111% (90% CI: 97–128%).

In contrast, pronounced differences in terms of the AUC(0–∞) and C_{max} values were determined in the case of CORAL® under fed vs. fasting conditions. The mean fed vs. fasted ratio for AUC(0–∞) was calculated as 144% (95% CI: 120–174%), and 317% (95% CI: 270–372%) for C_{max}. Accordingly, AUC(0–24) underlined the tremendous difference in the in vivo performance of the dosage form when switching from fasted to fed conditions, resulting in a mean ratio of 186% (95% CI: 157–220%).

The safety evaluation showed that, in total, 21 out of 27 subjects experienced 100 adverse events, and 84% of the events were reported to be at least possibly related to the study medication. The events comprised headache, back pain, substernal chest pain, asthenia, fever, tachycardia, phlebitis, syncope, thrombophlebitis, tooth pain, dyspepsia, gastro-enteritis, rhinitis, nausea, vomiting, increase in creatine phosphokinase, agitation, insomnia, pharyngitis, eczema, herpes simplex and ear pain. The type of adverse events observed here generally meet the expectations for a study under hospitalised conditions with a vasoactive drug compound, i.e. the predominant type of adverse events can be attributed either to the study conditions or can alternatively be explained by the vasodilatating effect of nifedipine. Nineteen out of 27 subjects (70%) suffered from headache, i.e. 72% of all adverse events were

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.

fastcase®
Smarter legal research.