An Open MonoCentre Study to Assess the Influence of Multiple-Dose Pioglitazone (AD-4833), 45 mg o.d., on Steady-State Pharmacodynamics and Pharmacokinetics of Phenprocoumon and Warfarin Enantiomers

Primary Objective: To evaluate the influence of a treatment with pioglitazone, 45 mg once dally at steady-state on the steady-state pharmacodynamics and pharmacokinetics of phenproeoumon and warfarin enantiomers.
Secondary Objeqfive: To evaluate the tolerability and safety of pioglitazone 45 nag in co-administration with phenprocoumon or warfarin.
Methodology: Open label, mono-centre study. Either phenprocoumon or warfarin was dosed for a total of 17 days aiming at steady-state concentrations, defined by its effects on prothrombin time on day 8 at the latest. Doses of phenprocoumon or warfarin were adjusted to reach and maintain a'Quick's value of 35 ± 5 %. Pioglitazone was co-administered at steady-state anticoagulant treatment with a dose of 45 mg once daily for 7 days.
Number of Subiects: In total, 24 subjects planned and analyzed of whom 12 subjects each for phenprocoumon and warfarin, respectively.
Duration of Treatment: 7 days continuous treatment with pioglitazone, at least 24 days either phenprocoumon or warfarin (up to 28 clays for 2 subjects).

Criteria for Evaluatior: Pharmacodynamics: Prothrombin time (PT, Quick's value) and its corresponding international normalized ratio (INR).
Pharmacokinetics: AUC0-h, Cmax (primary parameters derived from plasma concentrations of phenproeoumon and warfarin following multiple-dose phenprocoumon and warfarin treatment.

CONCLUSIONS
PHARMACODYNAMIC RESULTS:
There was no indication that pioglitazone 45 mg o.d. may change the pharmacodynamic effects of phenproeoumon or warfarin. Estimates for PT and INR ratios test/reference, i-e. with/without piogUtazone treatment, and their 90 %-confidence intervals were within the predefined range of equivalence [0.7, 1.43] during both phenprocoumon and warfarin steady state.
PHARMACOKINETIC RESULTS:
There was also no evidence for a relevant change in the pharmacokinetics of both enantiomers of phenprocoumon and warfarin, respectively. Estimates and their 90 %-confidence intervals were within the predefined range of equivalence [0.8, 1.25] for ratios with/without pioglitazone treatment when AUC0-24b of both enantiomers of phenprocoumon and warfarin are considered.

Co-administration of pioglitazone with either phenprocoumon or warfarin did not change the primary phannacodynamic or pharmacokinetic parameters of both phenprocoumon and warfarin.

Investigation of the effects of a single and repeated once daily doses of 45 mg pioglitazone (AD-4833) on the pharmacokinetics of digoxin at steady state serum concentrations. A randomized double blind two period cross-over trial

Primary objectives: To investigate the effect of a single and repeated doses of 45 lug pioglitazonc once daily on the pharmacokinetics of digoxin (0.25 mg o.d. maintenance dose) at steady state serum concentration.

Methodology: The trial was a randomized double-blind (with respect to pioglitazone and placebo), two period cross-over trial with a wash-out period of 14 days between the two periods, Healthy male Caucasian subjects, range of age 20-40 years, body mass index (BMI) of $\geq$ 18 kg/m2 and $\leq$ 25 kg/m2, written informed consent of the subject.

Number of subjects (planned and analyzed): 12 planned, 14 enrolled and randomized, 2 subjects discontinued due to personal reasons and 12 subjects completed the trial and were analyzed.

Duration of treatment: Digoxin: 0.25 ms b.i.d, on days 1 – 3, 0.25 mg o.d. on days 4 - 37
Pioglitazone: 45 mg o.d. (or placebo) on days 10 - 16 (period 1)
or on days 31 - 37 (period 2).

CONCLUSIONS
The 90% confidence intervals were within the predetermined range for digoxin AUC0-24 at single dose pioglitazone coadministration [92.14 - 112.94] and for digoxia Cmax for both, single dose and repeated doses pioglitazone conadminisration [84.94 - 134.03 and 101.43 - 133.98, respectively], Due to slight decrease of the digoxin AUC0-24h in the placebo group (12.18 pg.h/l to 11.24 pg · h/l), the 90% confident interval for AUC0-24h after repeated doses of piogUtazonc was slightly but clinically not relevantly above the predefined accepted range [103.94 - 127.17].

There is no clinically relevant interaction between single dose and repeated doses of 45 mS AD-4833 and repeated doses of 0.25 mg digoxin. The combination was safe and well tolerated in healthy subjects.

Evaluation of the influence of pioglitazone (AD-4833)-HCl 45 mg o.a.d, administration under steady state concentrations on the pharmacokinetic characteristics of a single oral dose of 1000 mg metformin-HCl in plasma and urine in a double-blind, placebo-controlled, cross-over study in healthy male subjects

Objectivns: Investigation on thc influence of pioglitazonc under steady state conditions after 8 days of treatment with 45 mg qd on the pharrnacokinetic characteristics of single oral dose of metformin I0/X) mg in plasma and urine.

Determination of the pharmacokinctic characteristics of pioglitazone and its two main active metabolites (M-HI, M-IV) in serum under steady state conditions and under coadmiuistration of a single dose of mefformin I000 mg. To assess the safety of · monotherapy with pioglitazone 45 rag o~d. and the concomitant administration of 1000 mg mefformin by laboratory examinations, vital signs, subjective findings/adverse events.

Methodology: A two-way cross-over study with repeated measurements of pharmacokine, tic and safety parameters during two :onsecutive treatment periods. The study procedure was double-blind for pioglitazone/plac~bo and open (not blinded) for metformin treatment. There was no wash-out phase..Number of subjects.

Test product, dose and mode of administration: Pioglitazone, 3 tablets of 15 mg, oral administration on study days 1-8 (period 1) or 9-16 (period 2) o.a.d. Oral administration (o.a.d.) of pioglitazone or placebo on study days1-8 (period 1) or 9-16 (period 2) placebo, oral administration of three tablets on study days' 1-8.

Statistical Methods:
Pharmacokinetics Listings of individual data (concentration-time data and pharmacokinetic characteristics of metformin and pioglitazone and its main metabolites) and descriptive statistics (arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, dispersion factor and coefficient of variation for the concentrations; and arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, dispersion factor, lower and upper confidence limits for the pharmacokinetic characteristics). Lack of interaction could be considered as an equivalence problem. Therefore, !ack of interaction could be concluded if the 90% confidence interval calculated from the error-term of the three-factorial ANOVA after log.transformation for thc ratio metformin with and without coadministration of pioglitazone was within the ranges of 0.8-1.25 for AUC and 0.70-I.43 for Cmax.

Criteria for Evaluation:
Primary Parameters: AUC., Crate, tla.x_z for mefformin in plasma and A¢~r~24a, fcurz.2~ for metformin in urine on study days g and 16
with and without pioglitazone comedicstion

CONCLUSIONS

There were no relevant differences in the single dose pharmacokinetic characteristics of metformin between pioglitazone under steady state conditions and placebo. All statistically tested parameters met the predetermined bioequivalence criteria. No relevant differences in the metformin amounts excreted in urine were found between the groups. These findings supported the results of metformin from plasma pharmacokinetics. The steady state pharmacokinetics of

pioglitazone were comparable to those reported in the literature.

AN OPEN LABEL PHARMACOKINETIC FOOD INTERACTION STUDY OF PIOGLITAZONE UTILIZING A 45 mg TABLET IN HEALTHY VOLUNTEERS (PNFP-036)

STUDY OBJECTIVE:	To evaluate the safety and determine the effect of food on the absorption of a 45 mg tablet ofpioglitazone.
STUDY DESIGN:	This was an open-label, two-treatment, two-period cross-over design study.
STUDY POPULATION:	A total of 23 subjects, 12 males and 11 females were enrolled in the study. Twenty-two subjects (II males and 11 females) completed the study (Subject No. 10 was discontinued by PI due to a pre-study laboratory abnormality; his Period 1 dose was the only dose taken).
STUDY DRUG:	Completed subjects received a single dose of 45 mg pioglitazone in each of two treatment periods in either a fasted or fed state.
CLINICAL PHASE:	Phase I
PK SAMPLING SCHEDULE:	Serum PK samples were collected at the following times: 0 hour (predose); 1, 2, 3, 4, 5, 6, 8, 12, and 16 hours after the administration of dosing on Day 1; and on the mornings of Days 2, 3, 4, and 7 at the same time of day as the 0 hour samples on Day 1.
SAFETY DATA SAMPLING SCHEDULE:	Clinical laboratory tests (including blood chemistry, hematology, and urinalysis) were performed at screening and on Days 0 (i.e., evening prior to dose), 3, and 7. Physical examinations were performed at screening and on Days 0, 4, and 7. Vital signs were recorded at screening and on Days 0, 2, 3, 4, and 7; 12-lead ECGs were performed at screening and on Day 0. Adverse events were recorded throughout the entire study. Subjects with adverse events were followed until the the event resolved or the condition stabilized.

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STUDY VARIABLES:

A. Pharmacokinetic

Model independent pharmacokinetic variables (e.g., Cm,~, Truax, AUC0.t, AUCo.~, terminal phase elimination/disposition rate constant, Tla, Clp/F, and Vd~JF) were calculated for pioglitazone (AD-4833), its metabolites M-III (AD-7932) and M-IV (AD-7925), and total (defined as sum of pioglitazone, M-III, and M-IV).

B. Efficacy

No efficacy variables were measured/calculated.

C. Safety

'Vital signs, 12-lead ECGs, clinical laboratory tests (hematology, blood chemistry, and routine urinalysis), adverse events, and physical examinations were performed.

STATISTICAL METHODOLOGY:

General:

Data listings were provided for pharmacokinetic and safety data. Summary statistics were provided, if applicable. Data analysis was to be performed using SAS for UNIX, version 6.12. The study population consisted of 23 subjects, 12 males and 11 females. All evaluable pharmacokinetic and clinical data fi.om the 23 subjects were analyzed.

Pharmacokinetic:

The pharmacokinetic variables were analyzed from serum samples. ANOVA statistical models, with gender, sequence, subject within sequence by gender, period, and treatment effects, were used to calculate confidence intervals for the comparison of the test (fed) and reference (fasted) groups and for the comparison of females (test) with respect to males (reference).

Efficacy:

No efficacy analysis was performed.

Safety:

Safety variables were summarized by descriptive statistics where applicable. Adverse events were summarized on the basis of treatment emergent adverse events. Adverse events and serious adverse events were presented by Sponsor-modified WHOART term and body system, by frequency, by relationship, and by maximum intensity.

Statistical Considerations:

All statistical tests were two-sided; 90% confidence intervals for gender were calculated across treatments and the 90% confidence intervals for treatment were calculated across genders. In order to identify changes in pharmacokinetic parameters of pioglitazone that might require a change in dosing, the Sponsor identified a 50% change as being clinically meaningful.

Sample Size Justification:

The sample size chosen for this study was based upon precedent set by other pharmacokinetic studies of a similar nature, not on statistical considerations.

PHARMACOKINETIC RESULTS:

Concentrations in serum of pioglitazone and the two metabolites, M-III (AD-7932) and M-IV (AD-7925), were determined by a validated high-performance liquid chromatography method with UV absorbance detection. The lower limit of quantitation was 25.0 ng/mL for pioglitazone, M-III, and M-IV. Serum levels for each subject at each time point were added for the three compounds to calculate the total (combined levels of pioglitazone, M-III, and M-IV). The mean (+ standard deviation, SD) pharmacokinetic parameters of pioglitazone, the two metabolites and the total and the 90% confidence intervals for the ratio of test (fed)/reference (fasted) are summarized below.

PIOGLITAZONE: SUMMARY OF PK PARAMETERS

PK	Test Mean' 45 mg tablet-fed	Reference Mean* 45 mg tablet-fasted	90% Confidence

Parameter	(Treatment A)	(Treatment B)	Test/Reference[b]	Interval
C,,,, (ng/mL)	1552 (+708.0)	1313 (:t:484.9)	118	(100, 130)[c]
Tm,~ (hou0	3.00[a] (2.00-5.00)[a]	2.00[d] (1.00-4.00)[a]	143	(124, 163)'
AUC0.t (ng*hr/mL)	13116 (+5630.5)	13484 (+5034.7)	97.3	(84.9, 107)[c]
AUCo4 (ng*hr/mL)	14071 (+5727.3)	15100 (4-5544.5)	93.5	(82.0, 103)[c]
K_t (hours'l)	0.0924 (~-0.04757)	0.0654 (:1.-0.03040)	141	(123. 160)[f]
TI_a (hour)	9.51 (+4.490)	13.8 (+8.47)	69A	(52.0, 86.7)[f]
Vd area/F (L/kg)	0.681 (—0.3189)	0.874 (i-0.4181)	77.6	(63.9, 91.3)[r]
CIdF (Idhr/kg)	0.0530 (:L-O.O 1953)	0.0478 (i-O.O 1490)	110	(97.5, 122)[f]

a Arithmetic mean :t: SD.
b Ratio ofuntransformed parameter means expressed as a percentage.
c 90% confidence interval for the natural log (In) transformed parameters.
d $Tm_{,x}$ is expressed as median with the range in parentheses.
e 90% confidence interval for T.u calculated using means and standard error from the ANOVA.
f 90% confidence interval for the untransformed parameter.
AUCo4 Area under the serum concentration time curve from Hour 0 to the last measurable serum concentration.
AUCo.~ Area under the serum concentration time curve to infinity.
C.,x Maximum serum concentration.
C!p/F Oral clearance.
Ke .Terminal phase elimination/disposition rate constant.
Ttt2 Terminal phase elimination/disposition half-life.
Tm,x Time to maximum serum concentration.
Vd area/F Apparent volume of distribution.

M-II!: SUMMARY OF PK PARAMETERS

PK Parameter	Test Mean' 45 mg tablet-fed (Treatment A)	Reference Mean' 45 mg tablet-fasted (Treatment B)	TestfReference[b]	90% Confidence Interval
Cmu (ng/mL)	181 (-+-39.8)	175 (+49.4)	104	(96.0. 117)[c]
Tmu (hour)	20.0[d] (8.00-24.0)[d]	20.0[a] (8.00-24.1)d	100	(85.5, 115)'
AUCo. t (ng*hr/mL)	7976 (5:1901.7)	7760 (±2148.4)	103	(95.4, 116)[c]
AUCo.~ (ng*hr/mL)	10581 (.+.3041.5)	10404 (+?858.9)	102	(92.5, 111)[c]
I~ (hours4)	0.0264 (5:0.00717)	0.0239 (+0.00748)	108	(96.6, 119)[t]
T_m (hour)	28.8 (±10.84)	32.1 (+11.34)	92.5	(76.4, 109)[f]

a Arithmetic mean ± SD.
b Ratio of untransformed parameter means expressed as a percentage.
c 90% confidence interval for the natural log (In) transformed parameters.
d T=ax is expressed as median with the range in parentheses.
e 90% confidence interval for Tmu calculated using means and standard error from the ANOVA.
f 90% confidence interval for the untransformed parameter.
AUCo-t Area under the serum concentration time curve from Hour 0 to the last measurable serum concentration.
AUCo-∞ Area under the serum concentration time curve to infinity.
Cmax Maximum serum concentration.
Ke Terminal phase elimination/disposition rate constant.
T1/2 Terminal phase elimination/disposition half-life.
Tmax Time to maximum serum concentration.

M-IV: SUMMARY OF PK PARAMETERS

PK Parameter	Test Mean' 45 mg tablet-fed (Treatment A)	Reference Mean" 45 mg tablet-fasted (Treatment B)	Test/Reference[b]	90% Confidence Interval
C,,u (ng/mL)	614 (-4-192.4)	571 (:1:166.4)	108	(96.7, 119)[c]
T,m (hour)	14,04 (5.00-24.0)[d]	16.04 (8.00-24.0)[d]	*85.5*	(73.1, 97.9)'
AUCe. t (ngehr/mL)	27130 (±7957.0)	27545 (:1:7973.1)	99.0	(91.3, 107)[c]
AUCo4 (ng*hr/mL).	32971 (5:9049.4)	33177 (5:8654.1)	99.8	(91.5, 108)[c]
I~ (hours[4])	0.0270 (t0.00748)	0.0259 (10.00623)	104	(97.0, 111)[r]
Tm (houO	27.8 (+8.64)	28.2 (:k6.59)	98.6	(88.5, 109)[r]

a Arithmetic mean :t: SD.
b Ratio of untransformed parameter *means* expressed as a percentage.
c 90% confidence interval for the natural log (in) transformed parameters.
d T.,,x is expressed as median with the range in parentheses.
e 90% confidence interval for Tau calculated using means and standard error from the ANOVA.
f 90% confidence interval for the untransformed parameter.
AUCo. t Area under the serum concentration time curve from Hour 0 to the last measurable serum concentration.
AUCo.~ Area under the serum concentration time curve to infinity.
C,,u Maximum serum concentration.
Kc Terminal phase elimination/disposition rate *constant.*
T_m Terminal phase elimination/disposition half-life.
T,.u Time to maximum serum concentration.

TOTAL: SUMMARY OF PK PARAMETERS

PK Parameter	Test Mean[a] 45 mg tablet-fed (Treatment A)	Reference Mean' 45 mg tablet-fasted (Treatment B)	Test/Reference[b]	90% Confidence Interval
C~,x (ng/mL)	1928 (+846.0)	1625 (+576.9)	118	(101,131)[c]
Truax (hou0	4-00[d] (2.00-5.00)~	3-03a (1.00-4.00)[d]	i 14	(100, 128)[c]
AUCo-t (ng* hr/mL)	49324 (+ 14368.8)	50350 (+ 14108.0)	98.5	(90.5, 107)[c]
AUCo.~ (ng*hr/mL)	56022 (+I 5651.0)	56810 (5:14606.6)	99.0	(90.6, 107)[c]
K, (hours'u	0.0306 (x~0.00705)	0.0298 (+0.00624)	103	(96.2, 109)[t]
Tv: (hour)	23.8 (--.5.74)	24.2 (+4.79)	98.8	(91.1,106)[t]

a Arithmetic mean 5: SD.
b Ratio of untransformed parameter means expressed as a percentage.
c 90% confidence interval for the natural log (In) transformed parameters.
d T=.~ is expressed as median with the range in parentheses.
e 90% confidence interval for T=u calculated using means and standard error from the ANOVA.
f 90% confidence interval for the untransformed parameter.
AUCo4 Area under the serum concentration time curve from Hour 0 to the last measurable sc;um concentration.
AUCo.oo Area under the serum concentration time curve to infinity.
Cm,x Maximum serum concentration.
Ke Terminal phase elimination/disposition rate constant.
Tm Terminal phase elimination/disposition half-life.
T,,,~ Time to maximum serum concentration.

SAFETY RESULTS:

During this clinical study, based on physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations (including hematology, blood chemistry, and urinalysis), there were no clinically significant findings that could be directly attributed to study medication. Of the 42 treatment-emergent adverse events (AEs) reported in this study, 40 were mild in severity and 2 were moderate in severity. Of the 42 treatment-emergent AEs reported during this study, the Principal Investigator judged that 30 AEs were not related to test material and the remaining 12 AEs were possibly related to test material.

In Vitro Protein Binding of Pioglitazone: Basic Studies

ABSTRACT

The protein binding of pioglitaz0ne has been studied *in vitro in* normal human serum and human serum albumin. The protein binding was determined by equilibrium dialysis at 37'C. Equilibrium was achieved in thirty minutes, and nonspecific binding to the cell and the membrane was negligible. Protein binding in normal human serum displayed a very small but significant dependence on pioglitazone concentration over the range of 0.034 to 2 ug/ml, and yielded a mean free fraction of 0.78 ± 0.009%. Protein binding to human serum albumin was not dependent on pioglitazone concentration and had a mean free fraction of 2.54 ± 0.089%.

The coefficient of binding for human serum was calculated to be 118.5 ± 1:2 and for human serum albumin 37.95 ± 0.83.

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In Vitro Protein Biding of Pioglitazone : II. Serum protein profile

ABSTRACT

The set-to protein binding profile of pioglitazone was studied by measuring time *relative binding, concentration* dependence, and coefficients of binding for three preparations of increasingly pure albumin, three glycoprotein fractions, and two lipoprotein. The three albumin fractions displayed the highest degree of binding to pioglitazone (>97%) and were concentration independent. The glycoproteins exhibited binding from 27-61% and displayed both sable and nonsaturable binding. Lipoprotein showed binding of about 75% and also displayed both saturable and nonsaturable binding characteristics.

In Vitro Protein Binding of Pioglitazone : III. Competitive Binding

ABSTRACT

The displacement of pioglitazone from human serum albumin by Coumarin, diazepam, U-90760, U-91322, and U-91324 was studied by equilibrium dialysis. All five compounds caused statistically significant displacement of pioglitazone from human serum albumin, but at varying degrees. In the presence of Coumarin at 200 uM, the coefficient of binding for pioglitazone decreased by 25.4%, and in the presence of 200 uM diazepam, the coefficient of binding for pioglitazone decreased by about 18.6%. In the presence of U-90760, U-91324, and U-91322 the coefficient of binding for pioglitazone decreased by 3.6%, 3.9%, and 4.8%, respectively. These data and previously generated data suggest that pioglitazone is bound somewhat selectively to site I on human serum albumin at the ethyl-pyridinyl end of the pioglitazone molecule.

Chiral Inversion of AD-4833 in Rat and Human Plasma

[redacted]

Summary

The chiral inversion of AD-4833 in rat and human plasma was investigated *in vitro and in vivo. The in vitro* chiral inversions between (+)- and (-)-enantiomers of AD-4833 occurred in plasma of rats and humans. At the equilibrium of the conversions, the enantiomer compositions ((+)/(-)) were about 4/6 and 1/1 for rat and human plasma, respectively. The inter-conversions of the enantiomers were also observed after the intravenous and oral administrations of AD-4833 to rats. The clairal inversion was expected to reach equilibrium before the completion of elimination from plasma. There were no obvious differences in the absorption and elimination between enantiomers. Because an *in vitro* chiral inversion was observed in human plasma, an *in vivo* chiral inversion was expected to occur at least in plasma when AD-4833 was administered to humans.

Identification of Human Cytochromes P450 Involved in the Metabolism of AD-4833 and the Effect of AD-4833 on the Activities of Human Cytochromes P450

Summary

In vitro study using microsomes from human B-lymphoblastoid cells expressing human cytochrome P450 (CYP) isoforms was undertaken to investigate the isoforms involved in the metabolism of AD4833 in humans. Microsomes expressing CYP1A1, CYP1A2, CYP2C8, CYP2C9 (Arg and Cys), CYP2C19, CYP2D6 and CYP3A4 were shown to metabolize AD-4833. The other CYP isoforms including CYP2A6, CYP2B6, and CYP2E1 were inactive for the metabolism of AD4833. AD-4833 was metabolized to M-IV, which was a major metabolite in human serum, by CYP1AI-, CYP1A2-, CYP2C8-, CYP2C9 (Arg and Cys)-, CYP2C19-, CYP2D6- and CYP3A4-expressed microsomes, and also to M-II by CYP2C8- and CYP2C9)(Cys)-expressed microsomes. These results suggest the contribution of the multiple CYP isoforms to the major metabolic pathway of AD4833 in humans. AD-4833 had no effect on the reactions mediated by microsomes expressing CYP isoforms at higher concentration than the therapeutic concentration. The results of this study indicate the little possibility for clinical drug interactions of AD4833 and co-administered drugs.

Contribution of Cytochrome P450 Isoforms to the Metabolism of Pioglitazone

Summary

Thc contribution ratios of the major cytochrome P450 (CYP) isoforms to thc metabolism of pioglitazone using individual human liver microsomes were determined by a multivariate regression analysis method. After seeking out the major metabolic pathway and the CYP isoforms which wore involved in the metabolism of pioglitazone in human hepatic microsomes, multivariate analyses incorporating the activities of the isoforms and the metabolizing rates wore carried out.

As a result, CYP2C8 and CYP3A4 were found to be major CYP isoforms, whose contributions to pioglitazone metabolism were sufficient but were comparable with the residual activity caused by the other isoforms. For the elimination of pioglitazone, the contributory ratios of CYP2C8 and CYP3A4 were 39.0 % and 17.0 %, respectively. Thus, the total activities of thc other CYP isoforms were also considered to have enough potentials to metabolize pioglitazone while each of them alone did not show any evident involvement. Because an adequate compensatory metabolism could be expected, the effect of concomitant drugs on the metabolism of pioglitazone was considered to be small, even if concomitant drugs occupied or inactivated one of the major CYP isoforms.