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RESEARCH**

APPLICATION NUMBER:

21-341

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name): Valdecoxib
PRODUCT (Brand Name): BEXTRA
DOSAGE FORM: Tablets
DOSAGE STRENGTHS: 10, 20 and 40 mg Tablets
NDA: 21-341
NDA TYPE: 1S
SUBMISSION DATE: 01/15/01, 4/10/01, 4/18/01, 8/13/01
SPONSOR: G.D. Searle & Co.
REVIEWER: Veneeta Tandon, Ph.D.
PHARMACOMETRICS REVIEWER: Jenny J. Zheng, Ph.D.
TEAM LEADER: Dennis Bashaw, Pharm.D.
OCPB DIVISON: DPE III, HFD 880
ORM DIVISION: ODE V, HFD 550

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RECOMMENDATIONS

From a pharmacokinetic standpoint the applicant has adequately defined the pharmacokinetics of both valdecoxib and its to-be-marketed dosage form. Thus, the Office of Clinical Pharmacology and Biopharmaceutics finds this portion of the NDA acceptable. Detailed labeling changes as suggested on page 29 should be conveyed to the sponsor. Additional labeling recommendations have been made to the Drug-Drug Interaction section (the drug interaction section of this NDA was reviewed as part of _____, see page 11 of the Review date 7/6/01 for these labeling comments), also appended to this current review. These labeling comments should be conveyed to the sponsor.

Because of the association between COX-2 inhibitors and cardiovascular side effects, further research to elucidate the interaction between aspirin and valdecoxib (i.e. the diminution of aspirin's anti-platelet effects) should be undertaken as this could be possible risk factor.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. _____

EXCECUTIVE SUMMARY

G.D. Searle is seeking approval of Valdecoxib, 10 mg, 20 mg and 40 mg tablets for the management of acute pain in adults, _____, primary dysmenorrhea, osteoarthritis and rheumatoid arthritis. The proposed dose for the treatment of acute pain in adults, _____ and primary dysmenorrhea is 40 mg once daily and that for osteoarthritis and rheumatoid arthritis is 10 mg once daily.

Valdecoxib is a cyclooxygenase-2 (COX-2)-specific inhibitor, a member of a larger class of nonsteroidal anti-inflammatory drugs (NSAIDs). COX-2 is an inducible form of cyclooxygenase that mediates both inflammation and localized pain response. By selctively inhibiting the formation of COX-2, it is theorized that inflammation/pain control can be achieved without the ulcerogenic side effects of non-selective NSAID.

Section 6 of the NDA 21-341 includes 31 pharmacokinetic studies that consist of general pharmacokinetics, bioequivalence studies, special population studies and drug-drug interaction studies. In addition to these in-vivo studies, there are several in vitro studies, a population analysis evaluating the covariates in osteoarthritis patients and a PK-PD analysis in _____ patients.

Analysis of the submitted studies indicates that valdecoxib has 83% oral bioavailability and displays linear pharmacokinetics across the therapeutic range. Concomitant administration of valdecoxib with a high fat meal resulted only in a delayed Tmax of 1-2 hours. Use of antacids did not have a significant impact on absorption. Like most NSAIDs valdecoxib is highly protein bound (~98%) and has a volume of distribution of 0.8 L/kg. It has a half-life of 8-11 hours and is primarily excreted in the urine as metabolites.

In regards to metabolites, valdecoxib is metabolized by multiple CYP P450 isoenzymes, including 3A4, 2C19, 2D6, 2C9, 1A2. The primary metabolite formed is a hydroxylation product identified as SC-66905 (M1).

A total of 13 in vivo drug-drug interaction studies were conducted, of these only fluconazole, ketoconazole and lithium were found to have clinically significant pharmacokinetic interactions with valdecoxib requiring dosing adjustment. When administering these drugs with valdecoxib, dosing with the lowest dose of valdecoxib and appropriate monitoring is recommended.

From a pharmacodynamic standpoint, significant drug-drug interactions were seen with warfarin (increased INR), aspirin (reduced effect on bleeding time), anesthetic agents (increased recovery times with propofol, alfentanil and fentanyl).

The pharmacokinetics of valdecoxib were assessed in the following special populations: Elderly males and females, hepatic insufficiency patients, and renal insufficiency patients (ongoing trial). Dosage reduction is recommended for both patients with moderate hepatic insufficiency and elderly females (less than 50kg). The use of valdecoxib in patients with severe hepatic insufficiency is not recommended.

The pharmacodynamic response of valdecoxib was assessed using the EC_{50} model. This model assesses onset of acute pain relief and is limited in regards to duration. Of the EC_{50} pain studies performed, 3 were designed to assess PK-PD relationships. From these studies valdecoxib was shown to be an effective acute analgesic over the dose range of 20-40 mg QD. The difference in response across the dose range was related more to duration than onset or peak pain relief. However, as EC_{50} pain model is not a good predictor of duration, the significance of these differences is unknown.

From a pharmacokinetic standpoint the applicant has adequately defined the pharmacokinetics of both valdecoxib and its to-be-marketed dosage form. The only outstanding issue is the relationship between valdecoxib, and COX-2 inhibitors as a whole, and an excess rate of cardiovascular events. Whether or not there is an underlying association between pharmacokinetics and these events is unknown. Additional research in this area needs to be evaluated for such information.

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QUESTION BASED REVIEW

(A) DRUG/DRUG PRODUCT INFORMATION

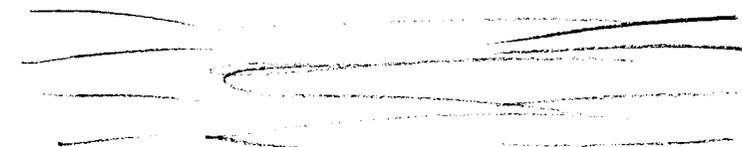
Dosage Form: Tablets, 10, 20 and 40 mg

Indication:

- For the prevention and treatment of acute pain in adults.
- For the treatment of primary dysmenorrhea.
- For relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis.

Dosage and administration (Sponsor's Proposed):

Management of Acute Pain in Adults: 40 mg once daily. On the first day of treatment, an additional 40 mg may be taken if needed.

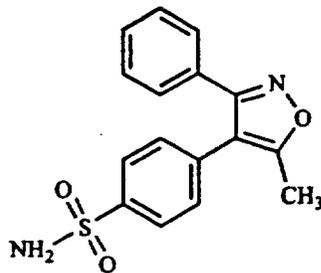


Primary Dysmenorrhea: 40 mg once daily. On the first day of treatment, an additional 40 mg may be taken if needed.

Osteoarthritis and Adult Rheumatoid Arthritis: 10 mg once daily. Some patients may receive additional benefit from 20 mg once daily.

Pharmacologic Class: Valdecoxib is a cyclooxygenase-2 (COX-2)-specific inhibitor, a member of a larger class of nonsteroidal anti-inflammatory drugs (NSAIDs)

Chemical Name: 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide and is a diarylsubstituted isoxazole. It has the following chemical structure:



Valdecoxib

Physical Characteristics: Valdecoxib molecular weight is 314.36, a white crystalline powder that is relatively insoluble in water (10 µg/mL)

Mechanism of action: The mechanism of action of valdecoxib is believed to be inhibition of COX-2-mediated prostaglandin synthesis. Valdecoxib inhibits production of both peripheral and central prostaglandins by COX-2, thereby reducing levels of these important mediators of pain and inflammation

Foreign marketing history: Not been marketed in any country

Formulation:

Ingredient	Purpose of Ingredient	Amount (mg) 10 mg tablets	Amount (mg) 20 mg tablets	Amount (mg) 40 mg tablets
Valdecoxib	Active ingredient	10	20	40
Lactose Monohydrate				
Microcrystalline Cellulose				
Pregelatinized Starch				
Croscarmellose Sodium				
Magnesium Stearate				
Purified Water				
Core Tablet Weight				
Film coated tablet weight		206	412	412

(B) GENERAL CLINICAL PHARMACOLOGY

What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

For Analgesia:

The primary measure of efficacy for the single dose assessments in pain studies was:

- Pain intensity differences, categorical scale (PID): PID scores were derived by subtracting the categorical pain intensity scores (PI) at each postdose time point from the baseline PI score.
- Other parameters are: Pain relief (PR): PR scores at each time point; Pain intensity difference (PRID): the sum of the categorical scale PID and the PR score at each time point; Time to onset of analgesia: the time to perceptible pain relief for patients who also registered a time to meaningful pain relief.

For Osteoarthritis:

The efficacy assessments are based on patient's and physician's global assessment of the arthritic condition and assessment of arthritis pain based on a visual analog scale and a questionnaire for the patient called the WOMAC osteoarthritis index.

For Rheumatoid Arthritis:

Efficacy endpoints include Tender Joint Count, Swollen Joint Count, Patient's global assessment, assessment of pain and physical function and duration of morning stiffness.

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

An exposure response relationship was established for analgesia. A pharmacodynamic (PD) model was developed to correlate pain relief (PR score) to valdecoxib concentration using logistic regression analysis. The efficacy end point in this analysis was the percentage of responders. Responder was defined as patients who received some pain relief from the use of valdecoxib. Two components, placebo and drug effects were included in this — pain model. The model suggests there is significant placebo effect for — pain relief and pain should be relieved eventually even without treatment. The drug effect was described by an Emax model. No delay exists between plasma and effect site. Using the model, at the dose of 40 mg, it was predicted that about 50%-68% and 68%-81% of the patients could receive some pain relief at 1 hour and 12 hours after the dose, respectively. About 74%-84% of the patients could receive some pain relief when maximal valdecoxib concentration achieved. The EC₈₀, which is the drug concentration at which 80% of the drug's maximal effect is achieved, are estimated to be about 0.118 and 0.134 µg/mL from two groups of studies. At a dose of 40 mg in study 035, the mean C_{max} was 0.502 µg/mL. The mean plasma concentration started to be above EC₈₀ at around 1 hour after dose and the concentration was above EC₈₀ until about 16-18 hours after the dose. No concentration-toxicity has been explored in this analysis.

The PD analysis showed that increasing dose higher than 20 mg will gain little effect in terms of percentage of responder. The association of toxicity with increasing dose was not explored in this analysis.

How long in time to the onset and offset of the pharmacological response or clinical endpoint?

The efficacy end point in the analysis was the percentage of patients who received some pain relief. The analysis showed that about 50%-68% of the patients received some pain relief at 1 hours after the dose and 68%-81% of patients still received some pain relief at 12 hours after the dose.

Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

The proposed dose for analgesia is 40 mg. However, the PD analysis suggested that the dose of 20 mg showed similar effect to 40 mg. At the dose of 40 mg, it was predicted that about 50%-68% and 68%-81% of the patients received some pain relief at 1 hour and 12 hours after the dose, respectively. About 74%-84% of the patients received some pain relief when maximal concentration reached. At the dose of 20 mg, it was predicted that about 50%-68% and 64%-76% of the patients received some pain relief at 1 hour and 12 hours after dose. About 71%-82% of patients received some pain relief when maximal concentration achieved. However, the observed data without PD modeling showed that about 41%-76% of the patients still received some pain relief at 12 hours after 40 mg dose but about 29%-67% of the patients received some pain relief at 12 hours after 20 mg dose, indicating that the pain relief effect may last longer at dose of 40 mg.

What are the general absorption, distribution, metabolism and excretion (ADME) characteristics of valdecoxib?

The general ADME characteristics were evaluated in radiolabeled studies. Drs. Lee and Bashaw have reviewed details of metabolism, distribution and elimination under NDA. Key points are summarized here.

Absorption:

- Valdecoxib is absorbed with peak concentrations achieved approximately 1.5-4.0 hours after oral administration.
- The primary compound in the plasma is valdecoxib, suggesting minimal first pass metabolism of orally administered valdecoxib.

Distribution:

- Valdecoxib is highly bound to plasma proteins (~98%) and the binding is linear with the therapeutic concentration range.
- There was extensive partitioning of total radioactivity into red blood cells, with valdecoxib red blood cell concentrations four-to five-fold greater than corresponding valdecoxib plasma concentrations.
- The steady state volume of distribution is approximately 80 L.

Metabolism and Elimination:

- Valdecoxib is extensively metabolized with less than 3% of the parent drug being present in the urine and feces, hence, valdecoxib is primarily eliminated via hepatic metabolism.
- There were 9 Phase I (oxidation and hydroxylation) and 5 Phase II (glucoronidation) metabolites identified.
- The primary active metabolite is SC-66905 (M1). There is a hierarchy of drug metabolism, as such the conversion of valdecoxib to SC-66905 (M1) is primarily mediated due to 3A4>2C19>2D6>2C9~1A2.
- Plasma concentrations of valdecoxib were 10-20 fold higher than the corresponding SC-66905 (M1) concentrations. SC-66905 is further metabolized, with less than 3% recovered in excreta. Therefore, efficacy is primarily derived from valdecoxib.

- Urinary excretion of metabolites is the major route of elimination. The major urinary metabolites are SC-66905 glucuronide and valdecoxib N-glucuronide.
- The elimination half-life of valdecoxib is 8-11 hours.
- The average plasma clearance is 6.0 L/hr.

The pharmacokinetic parameters for valdecoxib and M1 after single oral doses of commercial valdecoxib tablets is given in the following Table (from Study 077):

Single Dose PK Parameter by Analyte	Treatment Mean (% CV)		
	Valdecoxib 1x10 mg (N=27)	Valdecoxib 1x20 mg (N=28)	Valdecoxib 1x40 mg (N=28)
Valdecoxib			
AUC(0-lgc) (hr ng/mL)	1762 (33)	3405 (34)	6886 (33)
AUC(0-inf) (hr ng/mL)	1787 (33)	3450 (35)	6957 (34)
Cmax (ng/mL)	146 (28)	284 (28)	568 (29)
Tmax (hr)	3.41 (53)	3.22 (32)	3.08 (35)
T1/2 (hr)	8.31 (30)	8.53 (33)	8.84 (29)
CL/F (L/hr)	6.24 (34)	6.50 (34)	6.37 (31)
XU(0-72hr) (µg)	377 (25)	690 (43)	1321 (38)
SC-66905 (M1)			
AUC(0-lgc) (hr ng/mL)	142 (41)	287 (33)	580 (34)
AUC(0-inf) (hr ng/mL)	158 (38)	299 (31)	597 (33)
Cmax (ng/mL)	10.0 (33)	19.0 (32)	37.5 (36)
Tmax (hr)	4.78 (90)	3.93 (47)	3.61 (32)
T1/2 (hr)	9.08 (31)	8.45 (35)	8.92 (28)
XU(0-72hr) (µg)	36.0 (33)	65.9 (31)	133 (30)

What is the degree of linearity or nonlinearity in the dose-concentration relationship of valdecoxib based on its pharmacokinetic parameters?

After single dose:

- Following single dose, the kinetics of valdecoxib and SC-66905 (M1) are linear across the doses 1-400 mg.

After multiple dose:

- Following multiple BID dosing, linear kinetics exist for valdecoxib for the 2 mg and 5 mg valdecoxib BID dose groups, there is some deviation from linear kinetics in the 10 mg, 20 mg, and 50 mg valdecoxib BID dose groups. There could either be an increase in the bioavailability or decrease in clearance at multiple BID doses higher than 10 mg. SC-66905 follows linear kinetics across all dose groups.

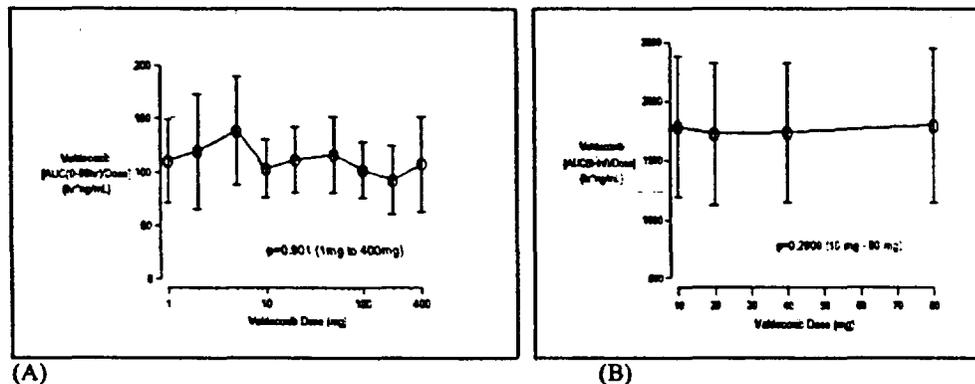
Does dose proportionality exist after single and multiple doses of valdecoxib?

Dose proportionality after single dose:

Dose proportionality after single oral doses of valdecoxib were examined in healthy volunteers in a dose escalation study and a dose proportionality study.

- Following single dose administration, valdecoxib, exhibits linear pharmacokinetics over the range of 1 to 400 mg (1, 2, 5, 10, 20, 50, 100, 200, 400 mg). The dose corrected AUC_{0-96} and AUC_{0-14c} show dose proportionality at doses over the range of 1-400 mg as shown in the following Figure A.
- The AUC_{0-96} and AUC_{0-14c} of its metabolite, SC-66905, also increase linearly with increasing doses of valdecoxib from 5 to 400 mg, but not linear in doses less than 5 mg.
- Another study demonstrated dose proportionality and linear pharmacokinetics following single doses of commercial tablets between 10 mg and 80 mg, as shown in the following Figure B.

Figure: Assessment of Dose Proportionality after a single dose



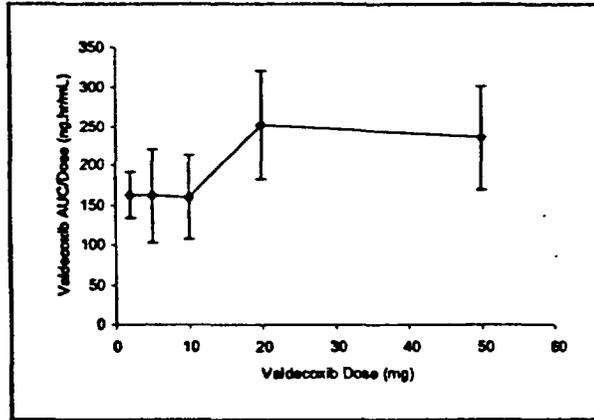
- Following single oral doses, the half life ranges from 5-10 hours.
- Peak plasma concentrations were achieved in 1.5-3.0 hours

Dose proportionality after multiple doses

The pharmacokinetics of multiple oral doses of valdecoxib were evaluated in a 10-day multiple rising dose study with BID dosing and a 7-day study with BID dosing of valdecoxib.

- From the first study, dose proportionality was observed within the BID dosing for 14-days for the 2-10 mg dose. But, there appeared to be a non-linear accumulation (20-45% increase in AUC) after 14 days of 20 or 50 mg BID dosing. This did not seem to be a true non-linear increase as the 20 mg and 50 mg doses had the same dose normalized AUC values, but there was a 45 % increase in exposure with the 20 mg dose as compared to the 10 mg doses. (See the following Figure C).

Figure: Assessment of Dose Proportionality after a BID dosing for 14 days
(C)



- From the second study, multiple twice daily doses of valdecoxib in the range of 5 mg to 20 mg were found to be dose proportional (see Table below). The disparity between the two studies cannot be explained. The sponsor is not recommending BID dosing for the intended indication of drug use, hence, the need of dosing adjustment with BID dosing may not be an important issue for this application.

Table: Dose Proportionality Assessment (Dose Adjusted PK Parameters After Single Dose Administration of Oral Valdecoxib)

Valdecoxib Plasma PK Parameter by Dosing Regimen	Least Square Means			p-Value from ANOVA
	Valdecoxib 5 mg (N=8)	Valdecoxib 10 mg (N=8)	Valdecoxib 20 mg (N=8)	
Analyte= Valdecoxib				
AUC(0-inf) (hr ng/mL)	198	167	175	0.481
Cmax (ng/mL)	16	12	14	0.526
Xu (0-48) (mcg)	50	55	52	0.772
Analyte= SC-66905				
AUC(0-inf) (hr ng/mL)	18	15	19	0.616
Cmax (ng/mL)	1.0	0.8	1.0	0.653
Xu (0-48) (mcg)	4	4.0	4.5	0.281

Table: Dose Proportionality Assessment (Dose Adjusted PK Parameters After Multiple BID Dose Administration of Oral Valdecoxib for 7 days)

Valdecoxib Plasma PK Parameter by Dosing Regimen	Least Square Means			p-Value from ANOVA
	Valdecoxib 5 mg (N=8)	Valdecoxib 10 mg (N=8)	Valdecoxib 20 mg (N=8)	
Analyte= Valdecoxib				
AUC(0-inf) (hr ng/mL)	332	341	371	0.571
Cmax (ng/mL)	26	24	26	0.918
Cmin (ng/mL)	10	11	12	0.375
Xu (0-48) (mcg)	75	105.0	115	0.310
Analyte= SC-66905				
AUC(0-inf) (hr ng/mL)	31	33	36	0.337
Cmax (ng/mL)	2	2.0	2.0	0.823
Cmin (ng/mL)	1.2	1.0	1.3	0.292
Xu (0-48) (mcg)	7.6	6.2	8.2	0.417

- Steady state valdecoxib levels were reached within 7 days of BID dosing of up to 50 mg doses.
- The mean terminal half-life of valdecoxib was 7-10 hours and increased within

this range with increasing doses.

- Valdecoxib has a prolonged absorptive phase, with T_{max} reaching at about 2-4 hours.

Do the pharmacokinetic parameters change with time following multiple dosing?

Based on the results of the single dose studies, the half life of valdecoxib with the 40 mg dose was approximately 9 hours and the pharmacokinetics were linear. With once daily dosing, significant accumulation is not expected. The accumulation factor was calculated to be 1.17. This 17% accumulation is not likely to be clinically significant.

However, with twice a day dosing for 14 days and a nonlinear accumulation of 20-45% was observed with 20 mg and 50 mg BID dosing. There seems to be an increase in bioavailability at higher doses for reasons that cannot be explained at this time.

Hence, multiple BID dosing with doses above 10 mg may lead to some degree of accumulation, but multiple QD dosing is not likely to lead to any clinically meaningful accumulation.

How does the pharmacokinetics of valdecoxib and SC-66905 in healthy volunteers compare to that in patients?

These trials were single dose trials. The pharmacokinetic parameters for valdecoxib and SC-66905 (M1) were generally similar between the healthy volunteers and the patients with ~~_____~~ pain at lower doses, however, the pharmacokinetic parameters were less than dose proportional as the dose of valdecoxib was increased. It has been shown earlier (Jamali et al, Br. J. Clin. Pharmacol. 1999 Apr; 47(4): 391-6) that stress after ~~_____~~ causes certain physiological changes that lead to reduced absorption and altered metabolism that lead to decrease in exposure and delayed absorption of certain NSAID (Ibuprofen). The decrease in exposure at higher doses of valdecoxib may be due to similar reasons.

The pharmacokinetics of valdecoxib and SC-66905 have been evaluated in patients with ~~_____~~ pain in 3 dose-ranging analgesia trials. These trials are part of the PK/PD analysis discussed elsewhere in this review.

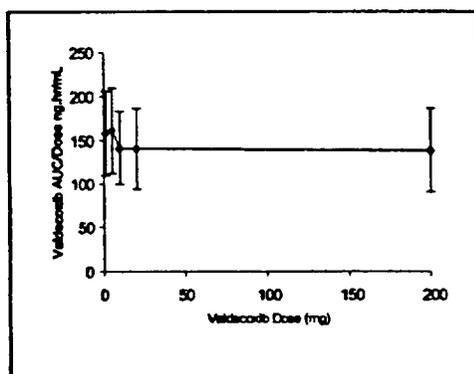
The following Table shows comparative pharmacokinetic parameters in the healthy volunteers and in patients.

Table: Pharmacokinetic parameters in healthy volunteers and patients with pain after single doses of 10, 20 and 40 mg valdecoxib tablets

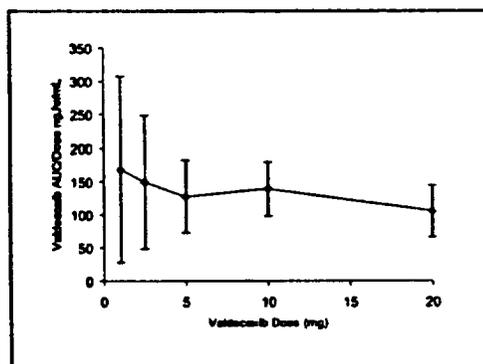
Valdecoxib Pharmacokinetic Parameters	10 mg Single Dose		20 mg Single Dose		40 mg Single Dose	
	Healthy (N=28)	Patients (N=51)	Healthy (N=28)	Patients (N=51)	Healthy (N=28)	Patients (N=51)
AUC ₀₋₂₄ or AUC _{0-∞} (ng.h/mL)	1787 (33)	1401.4 (24)	3450 (34)	2748 (29)	6957 (34)	4867.9 (35)
C _{max} (ng/mL)	146 (28)	167.8 (46)	284 (28)	330.2 (40)	568 (29)	502.9 (39)
T _{max} (hr)	3.41 (53)	2.60 (81)	3.22 (32)	2.50 (40)	3.08 (35)	3.1 (100)

Patient Data from Study 035, Healthy volunteer Data from Study 077

- A general trend of increase in T_{max} with the increase of dose was observed in patients, which was not so obvious in healthy volunteers.
- Both AUC and C_{max} for valdecoxib and SC-66905 (M1) increase approximately proportionately with single doses of 1-200 mg valdecoxib in patients, with proportionality being less apparent at higher doses. At higher single doses the exposure was less than dose proportional in patients. However, this trend was not observed in healthy volunteers after single dose of valdecoxib in the range of 1-400 mg. The dose proportionality from the 3 dose ranging studies in patients is shown in the following Figures in the dose range of 1-200 mg valdecoxib. All the 3 studies showed a decrease in exposure as the doses were increased, suggesting that the absorption of the drug is hindered at higher doses in patients or the metabolism is altered due the stress in such patients.



Study 005



Study 014

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Moderate hepatic impairment, gender and age were found to influence the exposure of valdecoxib to some extent.

Other patient factors including race, body surface area, time of most recent meal relative to dose, serum creatinine concentration, calculated creatinine clearance, SGOT, and SGPT either had effects that could be accounted for by age, sex and body weight or did not have statistically significant trends. These were evaluated in pharmacokinetic studies in the hepatic impaired and elderly subjects and also in a population analysis in patients with osteoarthritis of the knee.

Impact of Hepatic Insufficiency: (Taken from Dr. Bashaw's review)

- Valdecoxib can be used without dose reduction in the case of mild hepatic insufficiency.
- Patients with Child-Pugh score in the moderate range may need to have their doses reduced by approximately one-half. Among subjects with moderate impairment, mean C_{max} and AUC_{0-12} values following multiple dosing were approximately 130-142% higher compared to matched normal subjects.
- Because of the magnitude of increase in plasma levels seen in moderate hepatic insufficiency, valdecoxib should not be used in subjects with severe hepatic insufficiency.

Impact of Age and Gender: (from the Population analysis as well as Study 012 reviewed by Dr. Bashaw for _____)

- After correcting data for body weight differences, the oral clearance of valdecoxib showed a gradual but significant decrease with increasing age. The elderly subjects showed ~30% decrease in plasma clearance as compared to the younger subjects after a single 10 mg dose and after multiple 10 mg BID doses of valdecoxib. The C_{max} increased by 26-36% and AUC increased by 35-40% in the elderly subjects, compared to the healthy young subjects.
- A 38-43% reduction in renal clearance was observed in the elderly subjects as compared to the young subjects, paralleling a lower creatinine clearance in elderly versus younger subjects. The reduction in renal clearance in the elderly subjects is not likely to be important since renal excretion of valdecoxib and metabolites is very low, accounting for less than 5% of the total valdecoxib dose administered.
- Women had a 25% lower plasma clearance than men.
- Higher exposure in elderly women appeared to be due to both age and body weight factors, while higher exposure in men appeared to mostly due to age.
- Hence, elderly women or elderly patients with lower body weight (less than 50 kg body weight) should take the lowest recommended dose in the recommended dose range.

The following Table summarizes the apparent clearance after single or multiple doses of valdecoxib based on the intrinsic factors in the special populations as compared to healthy young adults.

Table: Single Dose or Steady State Apparent Plasma Clearance of valdecoxib in Special Populations.

Population	Study Number	No. of Subjects or Patients	Mean (% CV) Valdecoxib Plasma CL/F (L/hr)	Mean Change Relative to Control Group (Young Healthy Subjects)
Healthy young subjects (18 to 50 yr)	012	24	6.38 (31) (a)	Control
Healthy elderly subjects (65 to 86 yr)	012	23	5.05 (33) (a)	-21%
Males		12	5.85	-8%
Females		11	4.18	-34%
Hepatic impairment:	93-012			
Mild (41 to 72 yr)		9	6.89 (36) (b)	+ 8%
Moderate (41 to 62 yr)		11	3.56 (38) (b)	-44%
Renal impairment:	025			
Severe (37 to 45 yr)	(ongoing)	3	5.79 (34) (c)	- 9%
Hemodialysis (36 to 58 yr)		8	6.43 (45) (c)	+ 1%

(a) Valdecoxib plasma CL/F at steady state after multiple BID or QD doses of valdecoxib.

(b) Estimated valdecoxib plasma CL/F at steady state after multiple 10 mg BID

(c) Valdecoxib plasma CL/F after a single dose of valdecoxib.

This Table also shows that the elderly females and the moderately hepatic impaired patients have a markedly different plasma clearance, as compared to the healthy young adults.

Impact of Race:

Based on the population pharmacokinetic study in 242 Caucasians, 42 Blacks and 21 Others, race was not a significant covariate, hence, no dosage adjustment would be warranted for racial differences.

(D) EXTRINSIC FACTORS

The extrinsic factors were reviewed as part of the review of _____ the following section has been repeated in this review for the sake of completeness of the overall summary of clinical pharmacology and biopharmaceutics findings for this current NDA 21-341. For details, please refer to _____ review.

Were extrinsic factors investigated to assess their effect on the pharmacokinetics and pharmacodynamics of valdecoxib?

The sponsor has conducted several drug-drug interaction studies. No studies were conducted to determine the effect of herbal products, smoking or alcohol use.

Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes, the in vitro studies conducted using selected human CYP-450 enzymes or pooled human liver microsomes do suggest potential drug-drug interactions by and valdecoxib, especially with drugs that get metabolized by CYP2C9 and CYP2C19 and those that are inhibitors of CYP3A4 and CYP2C9.

This was based on the following observations from the in vitro studies:

- Valdecoxib is a substrate for CYP3A4 predominantly and also for CYP2C9 and CYP 2C19 to a lesser extent. *For details of in vitro metabolism studies, please refer to Dr. Sue Chih Lee's review for*
- The IC₅₀ and K_i values suggested potential inhibition of the CYP 2C9 isoform by and the CYP 2C19 isoform by valdecoxib and SC-66905 at projected therapeutic concentrations. The K_i value for valdecoxib toward CYP2C9 was much higher than the therapeutically relevant concentration of valdecoxib and the potential inhibition of this isoform by valdecoxib is unlikely.
- , valdecoxib or SC-66905 did not exhibit significant competitive inhibitory effects towards human CYP 1A2, CYP 3A4, CYP 2D6 and CYP 2E1 isoforms at therapeutically relevant concentrations. *For details of the in vitro inhibition studies please refer to Dr. Dennis Bashaw's review for*

In Summary,

Drug	Substrate	Inhibitor
Parecoxib	--	CYP 2C9
Valdecoxib	Primary: CYP 3A4 CYP 2C19 Secondary: CYP 2D6 CYP 2C9 Other: CYP 1A2	Primary: CYP 2C19 Secondary: CYP 2C9 Other: CYP 3A4 at higher levels and lesser extent CYP 2D6
SC-66905	--	Primary: CYP 2C19 Secondary: CYP 2C9 Other: CYP 3A4 CYP 2D6

Has the sponsor evaluated the possible drug-drug interaction studies based on the in vitro data?

Yes, the sponsor has evaluated the following substrates/inhibitors of the CYP 450 enzymes:

Isoenzyme	Substrates	Inhibitors
CYP 3A4	Midazolam Alfentanyl Fentanyl Glyburide Dextromethorphan	Ketoconazole Fluconazole
CYP 2C9	S-Warfarin Propofol	Fluconazole
CYP 2C19	R-Warfarin	Ketoconazole
CYP 2D6	Dextromethorphan	

However, the sponsor has not conducted in vivo interaction studies with a primary CYP2C19 substrate such as phenytoin. In vitro studies with S-mephenytoin and valdecoxib showed significant inhibition of CYP2C19, hence coadministration of such drugs should be done with caution.

Have the needs of NSAID class labeling been met with regards to the concomitantly administered drugs with parecoxib and valdecoxib?

The label does not specify co-administration with any particular drug. But NSAIDs usually interact with aspirin, methotrexate and lithium and the sponsor has evaluated the drug interaction of valdecoxib with these drugs. The other drugs that interact with NSAIDs are the ACE-inhibitors and Furosemide. The sponsor has not conducted studies with these drugs, but will get an NSAID Class labeling for these drugs. Since one of the intended usage of valdecoxib is the reduction of _____ pain with _____ administration of valdecoxib, the sponsor has evaluated a few anesthetic agents used for induction, such as propofol, midazolam, alfentanil and fentanyl.

Are there any in vivo drug interaction studies that indicate exposure and/or exposure-response are different when drugs were co-administered?

The following drugs as shown in the Table indicated a difference in exposure or the pharmacodynamic response when co-administered with either parecoxib or valdecoxib.

Interacting (I) Drug	NME Drug	I. Drug Dose SD/MD	NME Dose SD/MD	Pharmacokinetic Parameter	90% CI for PK	Change In Pharmacodynamic Measure
Warfarin	Parecoxib 10 mg BID	MD	MD	<u>S-warfarin</u> 4% ↓ in AUC 9% ↓ in Cmax <u>R-warfarin</u> 9% ↓ in AUC 13% ↓ in Cmax	(0.7,1.20) (0.75,1.11) (0.78,1.06) (0.75,1.02)	Slight ↑ in INR
Warfarin	Valdecoxib 40 mg BID	MD	MD	<u>S-warfarin</u> 12% ↑ in AUC 10% ↑ in Cmax <u>R-warfarin</u> 15% ↑ in AUC 14% ↑ in Cmax	(1.04,1.21) (1.02,1.20) (1.08,1.23) (1.06,1.22)	7% ↑ in mean INR from baseline mean

Interacting (I) Drug	NME Drug	I. Drug Dose SD/MD	NME Dose SD/MD	Pharmacokinetic Parameter	90% CI for PK	Change In Pharmacodynamic Measure
Aspirin	Parecoxib 40 mg BID	SD	MD	NA	NA	↓ in bleeding time increase
Propofol	Parecoxib 40 mg	SD	SD	<u>Propofol</u> 4% ↓ in AUC 10% ↓ in Cmax	(0.69,1.33) (0.52,1.55)	39% ↑ in time-to-return-to-baseline for sedation 22% ↑ in time-to-return-to-baseline for confusion
Alfentanil Fentanyl	Parecoxib 40 mg	SD	2 doses	<u>Alfentanil</u> No change in PK <u>Fentanyl</u> 8% ↑ in AUC 13% ↓ in Cmax	(0.91,1.29) (0.70,1.08)	↑ in anxiety, time-to-return-to-baseline anxiety, clumsiness ↓ in energy level and systolic blood pressure
Methotrexate	Valdecoxib 40 mg BID	SD	MD	<u>Methotrexate</u> 5% ↓ in AUC 19% ↓ in renal CL 27% ↓ in Xu 5% ↑ in plasma CL	(0.79,1.14) (0.55,1.20) (0.50,1.07) (0.87,1.27)	NA
Fluconazole	Valdecoxib 20 mg	MD	SD	<u>Valdecoxib</u> 62% ↑ in AUC 19% ↑ in Cmax 38% ↓ in CL <u>SC-66905</u> 25% ↑ in AUC 14% ↓ in Cmax, 43% ↑ in t1/2	(1.48,1.77) (1.08,1.30) (0.57,0.67) (1.16,1.36) (0.80,0.93)	NA
Ketoconazole	Valdecoxib 20 mg	MD	SD	<u>Valdecoxib</u> 38% ↑ in AUC 24% ↑ in Cmax 28% ↓ in CL <u>SC-66905</u> 23% ↑ in AUC 6% ↑ in Cmax	(1.27,1.50) (1.13,1.37) (0.67,0.79) (1.12,1.34) (0.97,1.16)	NA
Dextromethorphan	Valdecoxib 40 mg BID	SD	MD	<u>Dextromethorphan</u> 228% ↑ in AUC 111% ↑ in Cmax 78% ↑ in Xu <u>Total Dextromethorphan</u> 34% ↑ in AUC	(2.26,4.74) (1.69,2.62) (1.24,2.55) (1.28,1.41)	NA
Lithium	Valdecoxib 40 mg BID	MD	MD	<u>Lithium</u> 34% ↑ in AUC 33% ↑ in Cmax 25% ↓ in CL 30 ↓ in renal CL	(1.26,1.420) (1.26,1.40) (0.71,0.79) (0.62,0.79)	

Which drugs did not show a significant drug-drug interaction with either parecoxib or valdecoxib?

The following drugs as listed in the Table were evaluated, which did not show any drug interaction with parecoxib/valdecoxib.

Interacting (I) Drug	NME drug	I. Drug Dose SD/MD	NME Dose SD/MD
Midazolam (IV)	Parecoxib 10 mg IV	SD	SD
Midazolam (PO)	Valdecoxib 40 mg BID	SD	MD
Methotrexate* (PO)	Valdecoxib 10 mg BID	SD	MD
Glyburide	Valdecoxib 10 mg BID	MD	MD

*No drug interaction was observed with a lower dose (10 mg) of valdecoxib, but with a 40 mg dose of valdecoxib there was a 19% decrease in renal clearance of methotrexate.

When is dosage adjustment necessary?

Based on the information discussed above, dosage adjustment is necessary under the following situations:

- Patients with moderate hepatic impairment: Dose reduction by one half is recommended.
- Elderly female patients with low body weight: Dose reduction should be considered.
- Coadministration with fluconazole or ketoconazole: Dosing with the lowest dose is recommended.

(E) GENERAL BIOPHARMACEUTICS

What is the classification of valdecoxib as a drug, based on the Biopharmaceutics Classification System? What solubility and dissolution data support this classification?

BCS Class: Class IV (low solubility and low permeability)

Solubility: Practically insoluble in water, the solubility is 100 µg/mL at pH 7 and 25°C, solubility increases with increase in temperature and pH.

Permeability: Low, based on absolute bioavailability of 83%.

Dissolution: Not less than — (Q) in 45 minutes

What is in-vivo relationship of the proposed to-be marketed valdecoxib tablets to the Phase I, II and III (pivotal clinical trial formulation) in terms of comparative exposure?

The sponsor has used valdecoxib capsules in the Phase I studies. The capsules have been found bioequivalent to the Phase II tablets and those in turn to the Phase III tablets and finally the pivotal clinical trial tablets have been found bioequivalent to the to-be-marketed commercial tablets for the 10 mg 20 mg and 40 mg strengths.

Results can be summarized as:

- Oral formulations of valdecoxib used in clinical trials program are bioequivalent with respect to both valdecoxib and the metabolite SC-66905.
- Bioequivalence has been established between Phase III formulation and commercial formulation
- Bioequivalence has been established between 2x10 mg commercial tablets and 1x20 mg commercial tablets.
- Bioequivalence has also been established between 2x20 mg commercial tablets and 1x40 mg commercial tablets.

This has been shown schematically in the following Figures along with the 90% confidence intervals (acceptable between 80-125%) for the assessment of bioequivalence, which were all found acceptable. The bioequivalence studies were replicate design studies.

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Figure: Bioequivalence of Clinical Trial and Commercial Formulations of Valdecoxib 10 mg Dosage Forms.

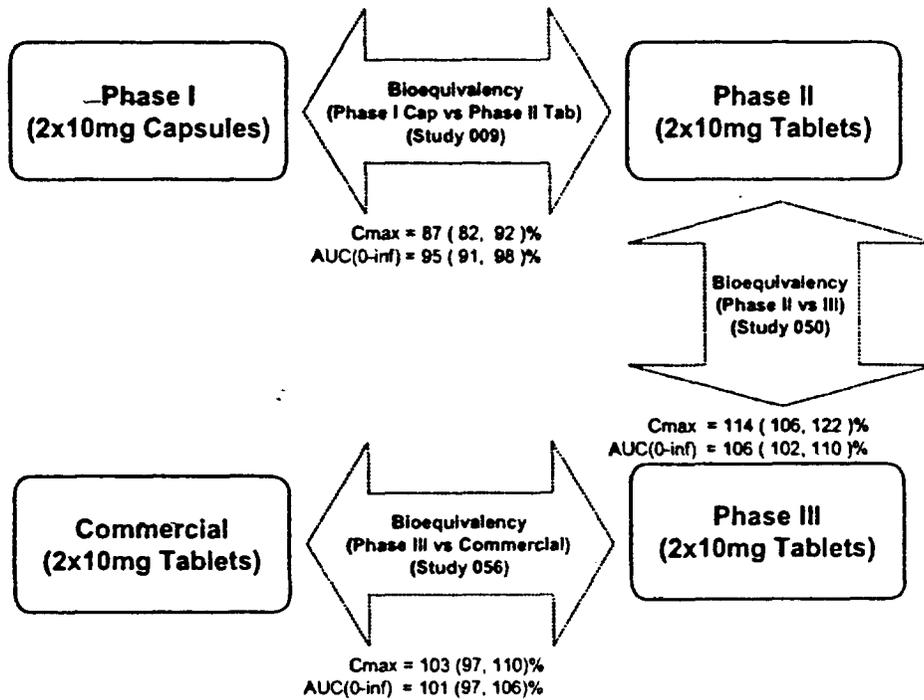


Figure: Bioavailability Links Between Valdecoxib 10 mg and 20 mg Commercial Tablets.

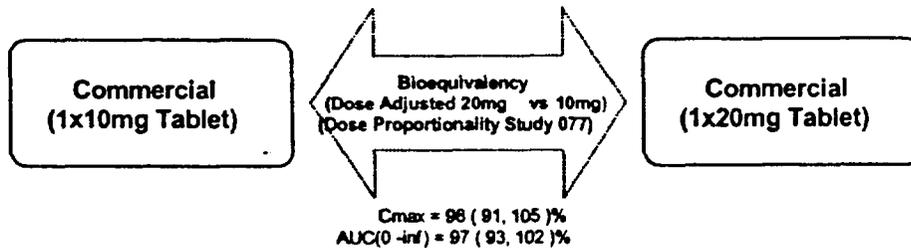
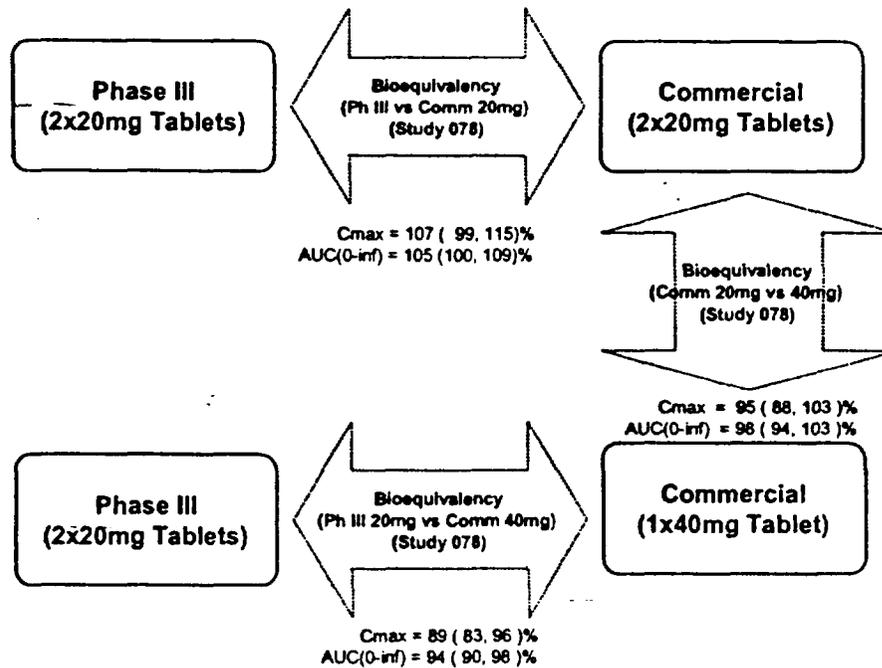


Figure: Bioequivalence of Clinical Trial and Commercial Formulations of Valdecoxib 20 mg and 40 mg Tablets.



Since replicate design bioequivalence studies were conducted, what information is available about variability and subject-by – formulation interactions?

Replicate design bioequivalence studies were conducted, but individual BE was not analyzed by the sponsor. FDA Analysis of the data was conducted using IBE, and the subject-by-formulation (SxR) interaction was found to be low or not present in two of the studies, as can be seen in the following Table. The magnitude of subject-by-formulation interaction is associated with the percentage of individuals whose average T and R ratios lie outside 0.8-1.25. In Study 056 the SxR interaction was 0.107 for AUC. Based on the current FDA guidance it is estimated that if SxR = 0.1356, then ~ 10 % of the individuals would have their average ratios outside 0.8-1.25.

The intra-subject variability was low too, but in Study 056 (Phase III vs. Commercial Tablets), the commercial tablets showed 60% higher variability as compared to the Phase III tablets.

Parameter	Formulation Comparison		
	Phase I Capsule vs. Phase II Tablet (Study 009)	Phase II tablet vs. Phase III tablet (Study 050)	Phase III tablet vs. Commercial tablet (Study 056)
AUCinf: Intra-subject variability Subject-by formulation Interaction	T: 13% R: 8.4% 0.00	T: 8.9% R: 14.2% 0.00	T: 9% R: 5.6% 0.107
C_{max} Intra-subject variability Subject-by formulation Interaction	T: 21% R: 11.6% 0.00	T: 12% R: 19.9% 0.118	T: 13.9% R: 16.7% 0.101

What is the absolute oral bioavailability of valdecoxib tablets?

The absolute oral bioavailability of valdecoxib is 83% (12%CV), suggesting low first pass metabolism. The incidence of adverse events following administration of oral valdecoxib was lower (22%) as compared to _____

What is the effect of food and antacid on the bioavailability of valdecoxib from tablet dosage form? What dosing recommendation should be made, regarding administration of the product to meals?

- High fat food and medium fat food have no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of valdecoxib
- The time to peak plasma concentration (T_{max}) is delayed by 1-2 hours.
- Administration of valdecoxib with antacid has no significant effect of either rate or extent of absorption.
- There is no significant food or antacid effects on the bioavailability of SC-66905 (M1), with the exception of statistically higher (20%) urinary excretion over 0-48 hours during the high fat regimen relative to the fasting regimen.

What is the effect of the _____ of the drug substance on the bioavailability of valdecoxib and its metabolite?

- A relationship was observed between the _____ of valdecoxib and in vivo drug absorption, whereby reductions in particle size generally resulted in increased rate (C_{max}) and extent (AUC) of valdecoxib absorption from the tablet dosage form.
- _____ has no apparent effect on conversion of valdecoxib to SC-66905.

- The large tablets were statistically bioequivalent to the clinical trial formulation.

Are the dissolution conditions and specifications adequately developed to assure in vivo performance and quality of the product?

Yes, the dissolution specifications are adequately addressed.

Dissolution Specifications/Method:

Apparatus: USP apparatus 2 (paddles)
Medium: 1% SDS unbuffered (w/v)
Volume: 1000 mL
Temperature: 37 °C
Paddle Speed: 75 rpm
Quantitation: —

Dissolution Specifications: Q= in 45 minutes

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APPENDICES

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APPENDIX B

INDIVIDUAL STUDY REVIEW

**SINGLE DOSE PHARMACOKINETICS IN HEALTHY SUBJECTS
& SINGLE DOSE PROPORTIONALITY STUDIES**

Study: N91-97-02-008: Pharmacokinetic studies of single oral doses of ¹⁴C valdecoxib and non radiolabeled valdecoxib in healthy male subjects

The purpose of this study was to determine the absorption, distribution, metabolism and elimination (ADME) profile of [¹⁴C]valdecoxib 50 mg suspension and unlabeled valdecoxib 50 mg capsule. Only the ADME characteristics of valdecoxib will be discussed here. Given the dosage form of this application being tablets, the comparative pharmacokinetics of the suspension and capsule will only be discussed very briefly. The study design is as follows:

Study Design	Two phase, two period, single dose, crossover
Study Population	N=8 healthy Caucasian subjects, 2 in pilot phase and 6 in randomized phase. 8M, Ages 20-50, weight 66.6-82.5 kg
Treatment Group	A: [¹⁴ C]Valdecoxib ~ suspension B: Valdecoxib solid oral capsule
Dosage and Administration	A: 50 mg [¹⁴ C] (specific activity 1.99 µCi/mg, lot RCT 10405), reconstituted in overnight fast B: 50 mg capsules, lot RCT 10447. Consumed 180 mL water 1, 2 and 3 hours postdose, overnight fast
Sampling: Blood	For Valdecoxib, SC-66905 and SC 67817: At predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose. Additional blood samples were collected 60 and 72 hours postdose following [¹⁴ C] Valdecoxib administration.
Urine	For [¹⁴ C] Valdecoxib treatment only: measurements at -12-0 hrs predose, 0-1, 2-3, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 hrs postdose.
Feces	For [¹⁴ C]Valdecoxib treatment only Up to 216 hours post dose
Analysis	

Observations:

Radioactivity in Plasma:

The pharmacokinetic analyses for the radioactivity in plasma is shown in the following Table:

Table: Pharmacokinetic Parameter for Radioactivity Analyses

AUC (0-t) (ng equiv*hr/mL)	16,100
AUC (0-∞) (ng equiv*hr/mL)	25,200
C _{max} (ng equiv/mL)	1,040
T _{max} (hr)	1.7
K _e (1/hr)	0.0135
T _{1/2} (hr)	66.6

- In plasma, the primary compound identified was the parent, valdecoxib, which accounted for 70-85% of the recovered radioactivity. This suggested minimal first pass metabolism of orally administered valdecoxib.
- In addition, minor peaks of SC-66905 (M1) were identified (3-8% of the radioactivity).
- Plasma concentrations of valdecoxib were 10-20 fold higher than corresponding SC-66905 (M1) concentrations.
- The maximum concentration of radioactivity in plasma following a single oral dose of [¹⁴C]valdecoxib ranged from 880 to 1170 ng equivalents/mL and was reached between 0.5 and 3 hours postdose.
- T_{1/2} values for total radioactivity ranged from [redacted] with a mean of 66.6 hours.
- There was extensive partitioning of total radioactivity into red blood cells, with valdecoxib red blood cell concentrations four-to five-fold greater than corresponding valdecoxib plasma concentrations.

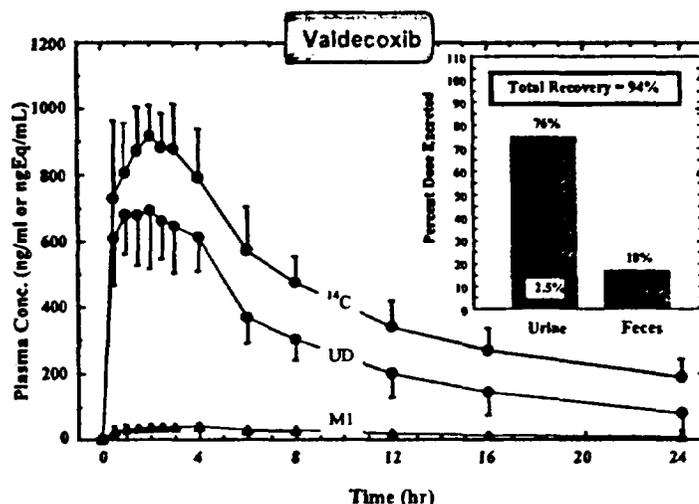
Excretion of Radioactivity in Urine and Feces

- In this study, valdecoxib was extensively metabolized with less than 3% of the parent compound was recovered in urine.
- Most of the [¹⁴C]valdecoxib was absorbed from the gastrointestinal tract into the general circulation and urinary excretion was the major elimination route.
- Nine metabolites (M1 through M9) were identified in the urine. These metabolites were formed via Phase I hydroxylation and oxidation reactions. In addition, Phase II metabolism resulted in glucuronide conjugates of valdecoxib (19.5%), and the SC-66905 (M1-G, 23.3%), SC-76082 (M2-G, 6.68%), M3 glucuronide (M3-G, 9.48%), and M5-G and M9-G metabolites. Each of the remaining metabolites accounted for less than five percent of the radioactivity.
- In feces, trace amounts (less than 1%) of the radioactivity were detected as valdecoxib, SC-66905 (M1) and M3.
- The total excretion of radioactivity in urine and feces was 94.1%, ranging from 87.9% to 100% among the eight subjects. Approximately 76% of the radioactivity was recovered in urine and 18% of the radioactivity was recovered in feces.

- The majority of the radioactivity excreted was excreted by 48 hours postdose in urine and by 96 hours postdose in feces.

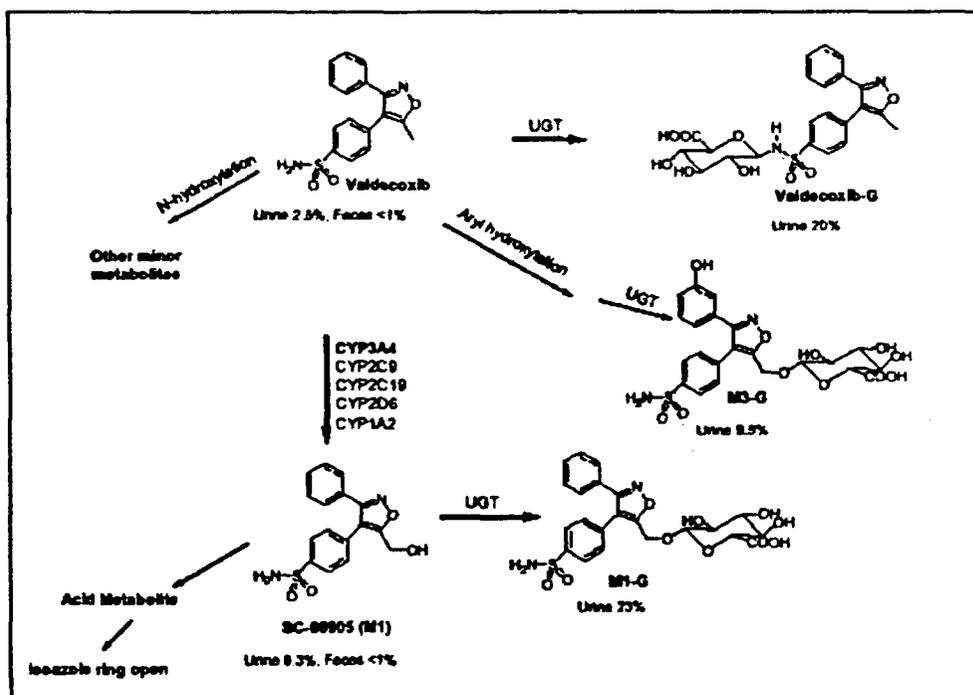
This information can be shown graphically in the following figure:

Figure: Mean \pm SD (N=8) Plasma Concentration-Time Curves of Total Radioactivity (14 C), Unmetabolized Drug (UD) and SC-66905 (M1), and Recovery of Total Radioactivity in Urine and Feces (Inset) after a Single 50 mg Oral Dose of [14 C]Valdecoxib Suspension.



The proposed metabolic pathway of valdecoxib in humans is shown in the following flow diagram

Figure: Proposed metabolic pathway of valdecoxib in humans



Valdecoxib and SC-66905 Pharmacokinetics:

- Both valdecoxib and [¹⁴C]valdecoxib were readily absorbed. As expected, peak valdecoxib plasma concentrations were achieved more quickly with the oral suspension (1.5 hours) compared to the oral capsule (3.2 hours), as shown in the following figure:

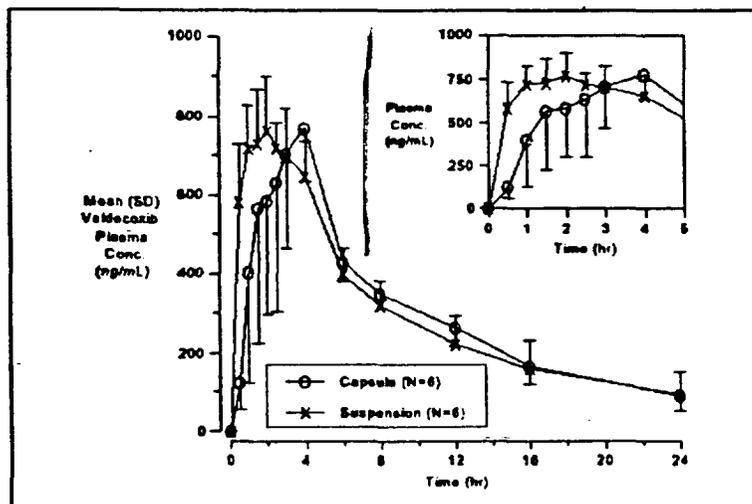


Figure: Valdecoxib Plasma Concentrations in Six Healthy Subjects Between 0 and 5 Hours (Inset) and Between 0 and 24 Hours after Single 50 mg Doses of [¹⁴C]Valdecoxib Suspension (X) and Capsule (O) Under Fasting Conditions.

Conclusions:

- Valdecoxib is extensively metabolized with less than 3% of the parent drug being present in the urine and feces.
- Urinary excretion is the primary route of elimination. The major metabolites are SC-66905 glucuronide and valdecoxib N-glucuronide.
- Valdecoxib has extensive partitioning into the red blood cells.
- In plasma, the primary compound identified was the parent, valdecoxib, which accounted for 70-85% of the recovered radioactivity. This suggested minimal first pass metabolism of orally administered valdecoxib.

Study N93-97-02-008: Pharmacokinetics of single IV doses of [¹⁴C]parecoxib and non radiolabeled valdecoxib in healthy subjects

Only plasma pharmacokinetic parameters from the oral administration of valdecoxib will be discussed here. Parameters pertaining to _____ will not be discussed here, as an individual application for _____ has been submitted earlier _____ and reviewed.