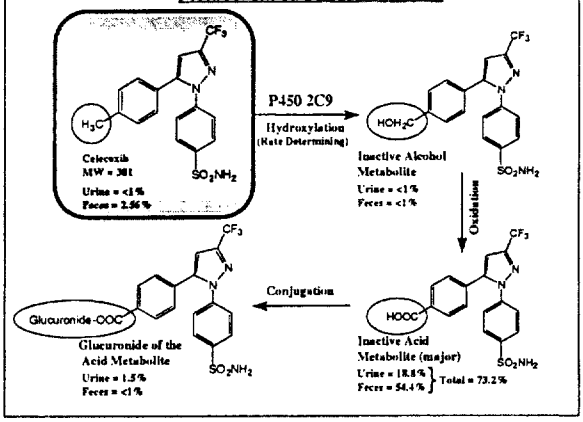
Celecoxib: Clinical PK

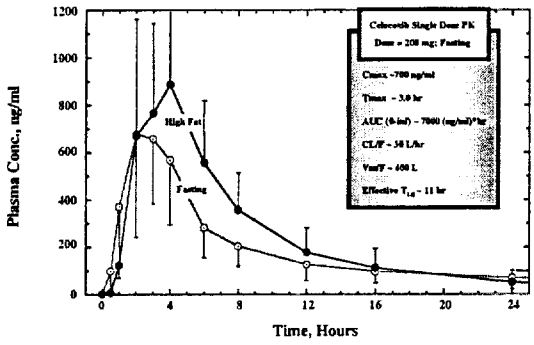
1. Basic PK Profile
2. PK in Special Populations
3. Drug-Drug Interactions
4. Population PK/PD Analysis of Pivotal Clinical Trial Data
5. Bioequivalency: Clinical Trial Batches vs. Commercial Formul.

Celecoxib PK Assessed In 1566 Subjects From 32 Studies

Metabolism of Celecoxib in Man



Mean (SD; N = 24) Plasma Concentrations of Celecoxib Following 200 mg Single Doses Given Under Fasting State or With High Fat Breakfast



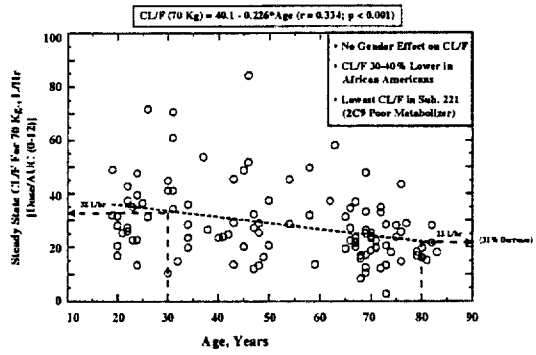
Celecoxib: Clinical PK

PK in Special Population

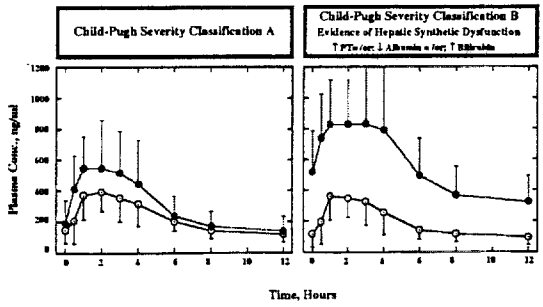
1. Effect of Age, Gender, Weight and Race
2. Effect of Hepatic Impairment
3. Effect of Chronic Renal Impairment
4. Effect of Diabetes (NIDDM)
5. Effect of Osteo- and Rheumatoid Arthritis

Relationship Between Celecoxib CL/F (Adjusted For 70 Kg) and Age (N=112)

[-010 Renal Elderly; -015 Young vs. Elderly PK; -017 MTX Interaction; -043 BID vs QD PK]



Mean (SD; N = 11-12) Steady State Plasma Conc.-Time Curves of Celecoxib in Hepatic Impaired Patients (●) and Matching Healthy Subjects (○) Following Celecoxib 100 mg BID

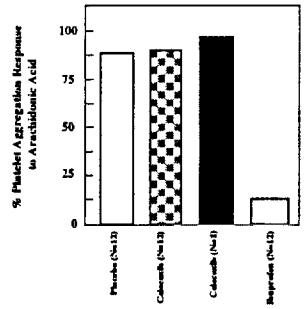


Six Subjects (Out of 1566) Showing Unusually High Exposure of Celecoxib

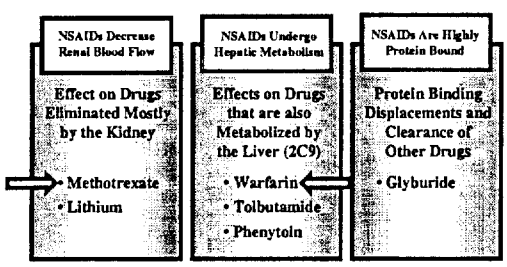
Subject	Study	Age (Years)	Weight (kg)	Sex	Race	Dose (BID) (mg)	AUC (tau) (ng/ml*hr)	CL/F (L/hr/70 kg)	Cmax (ng/ml)
221	-015	73	74.9	F	Caucasian	200 (7 days with food)	72.2	2.59	10.2
222	-015	68	79.3	F	Caucasian	200 (7 days with food)	21.4	8.25	3.20
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
031	-072	33	70.1	M	Caucasian	200 (Single Dose)	54.6 (lqc)	3.66	2.84
827	-824	68	56.2	F	Afr. Amer.	100 (7-10 days)	NA	NA	2.39
461	-824	80	71.9	F	Afr. Amer.	200 (7-10 days)	NA	NA	5.97

Note: Subject #012, study -065 and subject #031, study -072 were the same subject participating in two different studies

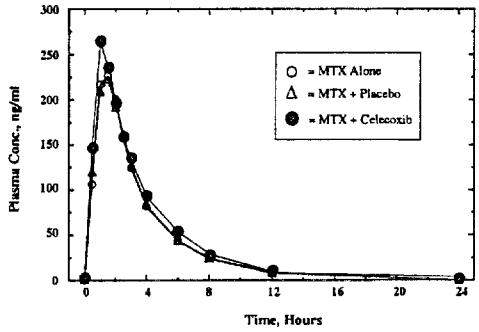
Mean (N=12) Steady State COX-1 Mediated Pharmacodynamic Responses at Two Hours on Day 8 Following Celecoxib (600 mg BID), Ibuprofen (800 mg TID) or Placebo
Study N49-97-02-065



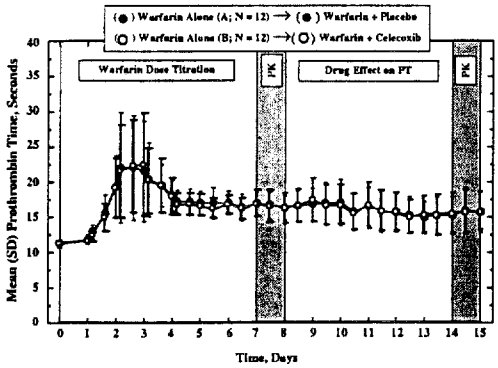
Drug-Drug Interactions



Mean (N = 14) Methotrexate (MTX) Plasma Conc. In Patients Following Their Usual Therapeutic Doses of MTX (5-15 mg Weekly) Given Alone, and After 7-Day Treatments With Placebo (BID) or Celecoxib (200 mg BID)



Effect of Celecoxib 200 mg BID on Pharmacodynamic Response (Prothrombin Time) to Warfarin QD



Celecoxib: PK Summary

- Achiral, Low-Solubility-High-Permeability Drug With Systemic Availability of ~73%
- CL/F ~500 ml/min (~30 L/hr); Vss/F ~400 L; Effective $T_{1/2}$ ~11 hr; Extensive Hepatic Metabolism To Inactive Metabolites via P450 2C9; Protein Binding ~97% and Concentration Independent
- Advantages of Dosing With or Without Food and Potential For Once a Day Dosing
- Lower CL (higher AUC) in Elderly Women (Lower Body Weight), in Patients With Moderate to Severe Hepatic Impairment and in African Americans
- Lack of Drug-Drug Interactions Commonly Encountered With NSAIDs (MTX, Lithium, Warfarin, Phenytoin, Glyburide, Tolbutamide)