CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-998

PHARMACOLOGY REVIEW(S)

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA	**20-998**
DRUG:	Celecoxib; Celebrex™; SC-58635
SPONSOR:	G.D. Searle & Co. 4901 Searle Parkway Skokie, IL 60077
SUBMISSION DATE:	June 29, 1998
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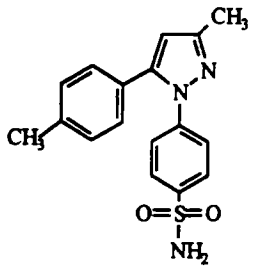
DRUG CATEGORY:	Nonsteroidal Anti-inflammatory & Analgesic [Inhibitor of Cyclooxygenase 2 (COX-2)]
FORMULA:	4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide ($C_{17}H_{14}F_3N_3O_2S$); M.W.: 381.38

INGREDIENTS	QUANTITIES (MG)	
	100 mg Capsule	200 mg Capsule
Celecoxib	100	200
Lactose, NF		
Na Laury Sulfate, NF		
Povidone, K29-32		
Croscarmellose Na, NF		
Mg Stearate, NF		
Purified H_2O, USP		



SC-58635

CAS Nº:	169590-42-5
INDICATION:	For acute and chronic treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis; and for the management of acute and chronic pain.
DOSAGE FORM:	Capsules, 100 and 200 mg
RELATED DRUG/INDs/NDAs/DMFs:	

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1. PHARMACOLOGY

1.1. OVERVIEW

The actions of currently available NSAIDs in the market to inhibit the production of prostaglandins (PGs) by cyclooxygenases (COX) can be divided into three categories: (i) modification of the enzymes by acetylation of a serine residue at the active site, such as aspirin; (ii) induction of time-dependent irreversible inhibition of enzymes, such as indomethacin or flurbiprofen; (iii) induction of reversible competitive inhibition, such as ibuprofen and mefenamate. Two distinct COX enzymes were identified recently. COX-1, a constitutively expressed form, displays in gut and kidney that produce PGs which are required for normal physiological functions. COX-2, an inducible isoenzyme, is encoded by a different gene from COX-1 and only exists in high concentrations under the inflammatory condition or following mitogenic stimulation. COX-1 mRNA could be detected in all tissues with highest expressed levels found in platelets, vascular endothelial cells, liver, stomach, spleen, kidney collecting tubules and colon. In contrast, COX-2 mRNA levels were extremely low in all normal tissues except rat brain. Both enzymes have approximately 60% homology and are able to convert arachidonic acid to PGH_2 with similar affinity. The amino acid residues thought to be essential for this enzymatic conversion are conserved in both structures.

GI toxicity, a common side effect of NSAIDs, is believed to be caused by the inhibition of PGs which were regulated by COX-1 in the GI tract and required for normal physiological function. The present submission introduced celecoxib (SC-58635 - $C_{17}H_{14}F_3N_3O_2S$), a newly developed COX-2 inhibitor, which is a diarylsubstituted pyrazole compound. The physical interactions between celecoxib and COX-2 are illustrated in the above figure (1.5 13). Celecoxib is proposed for the treatment of the signs and symptoms of RA and OA, and for the management of acute and chronic pain.

1.2. GENERAL AND MECHANISM-RELATED PHARMACOLOGY

1.2.1. IN VITRO SELECTIVITY FOR COX-2 (REF. 1-3, 5, 6, 11, 13)

- Inhibition of PGE_2, TXB_2, or LTB4 Production by Human Fetal Skin Fibroblasts or Whole blood -

	SC-58635 IC_{50} (μM)			
Cell Type	Human Fetal Skin Fibroblast	Human Whole Blood		
	IL-1 Induced COX-2 Mediated PGE_2 Production	A23187-Induced COX-1 Mediated TXB_2	5-LO[a] Mediated LTB4	LPS-Induced COX-2 Mediated PGE_2 Production
Expt. 1	0.3 ± 0.1 (n=7)	1.6 ± 0.3 (n=6)	2.4 ± 0.5 (n=4)	0.139 ± 0.04 (n=4)
Expt. 2	-	6.665 ± 1.081 (n=3)	-	0.164 ± 0.06 (n=7)

[a] 5-LO = 5-lipoxygenase

- Inhibition of O_2 Consumption and Peroxidase -

Parameters Measured	IC_{50} (μM)	
	Sheep COX-1	hCOX-2
Oxygen Consumption	50	0.2
Peroxidase Activity	10	0.2

- Inhibition of PGE_2 Production Mediated by Recombinant COX-1 and COX-2 -

Treatment	IC_{50} (μM)	
	hCOX-1	hCOX-2
Indomethacin	0.1 ± 0.07 (n=147)	1.10 ± 0.50 (n=148)
SC-58635	15 ± 3.40 (n=7)	0.04 ± 0.01 (n=7)
SC-59046	36 ± 13.0 (n=9)	0.05 ± 0.02 (n=10)

- *Ex Vivo* Inhibition of A23187-induced COX-1 Mediated TBX2 Production by Rat Whole Blood -

Treatment	Dose (mg/kg)	Route	Duration (day)	A23187-induced TBX2
SC-58635	10, 30	po	1	↔ (no effect)
	15 bid	po	1	↔
	600	po	3 or 7	↓ 60-70%
Indomethacin	5	po	1	↓ 93%
	4	po	7	↓ >99%

- Inhibition of PGE_2, TXB_2, or LTB4 Production by Dog Whole blood -

Treatment	IC_{50} (μM)	
	AA-Induced COX-1 Mediated TXB_2 Production	LPS-Induced COX-2 Mediated PGE_2 Production
SC-58635	1.96 ± 0.59 (n=4)	0.46 ± 0.13 (n=9)
SC-59046	2.32 ± 0.57 (n=4)	0.20 ± 0.07 (n=3)
Indomethacin	0.16 ± 0.05 (n=4)	0.28 ± 0.08 (n=6)

AA = arachidonic acid

1.2.2. In Vivo Selectivity For Cox-2 (Ref. 5, 7, 10, 15)

- In Vivo Effects on Tissue PGE_2 Levels

Study	Species N#/group	Dose/Route/Duration	Observations
Carrageenan Induced PGE_2 Production in PGE_2 in Carrageenan Induced Air Pouch and Stomach	♂ Lewis Rat 5/group	0.1-10 mg/kg ig	Dose-dependent ↓ of PGE_2 and 6-keto $PGE_{1\alpha}$ with an ED_{50} of 0.2 ± 0.1 mg/kg.
	♂ Fasted Lewis Rat 6/group	0.1-200 mg/kg po	Dose-dependent ↓ of PGE_2 in subcutaneous air pouch with an ED_{50} of 0.97 ± 0.1 mg/kg. Non-dose dependent ↓ of stomach PGE_2 production by 20-40% at all doses.
PGE_2 in Various Tissues	♂ Rat, 6/group	600 mg/kg/day po x7	↓ PGE_2 in kidney (65.6%), stomach (48%), stomach mucosa (59.1%), duodenum (38.5%), caecum (58.5%), and colon (32.3%).
	♀ Rat, 8/group	600 mg/kg/day po x3 or x7	↓ PGE_2 in stomach (53%), stomach mucosa (53-60%), duodenum (28.8%), and colon (54-63%).
PGE_2 in CFS	♂ Lewis Rat Adjuvant Arthritis	0.3, 3, or 10 mg/kg po	0.3 mg/kg - ↓ PGE_2 by 94% at 4 hr and 75% at 8 hr post dose. ≥3 mg/kg - completely ↓ PGE_2.
PGE_2 Paw Exudate/Synovial Fluid			0.3 mg/kg - ↔ on PGE_2 in paw exudate. 3 mg/kg - ↓ PGE_2 by 49% at 4 hr and 34% at 8 hr post dose. 10 mg/kg - ↓ PGE_2 by 61% at 4 hr and 81% at 8 hr post dose.

1.3. *In Vivo* Effects Related to Proposed Therapeutic Indications

1.3.1. Anti-Inflammatory Effects (Ref. 7, 8, 14)

Models	Species	Dose(mg/kg)/Route	Observations
Carrageenan Induced Paw Edema	♂ SD rats	2-100 mg/kg ig	Dose-dependent ↓ paw edema with an ED_{50} of 7 ± 1 mg/kg.
Adjuvant Arthritis	♂ Lewis Rat	0.03-3 mg/kg bid ig x10	Dose-dependent ↓ paw edema with an ED_{50} of 0.3 ± 0.1 mg/kg.
Carrageenan Induced PGE_2 Production in Air Pouch	♂ Lewis Rat	0.1-10 mg/kg ig	Dose-dependent ↓ of PGE_2 and 6-keto $PGE_{1\alpha}$ with an ED_{50} of 0.2 ± 0.1 mg/kg.
Adjuvant Arthritis	Lewis Rat	1 mg/kg po x10	↓ synovial inflammation (21%), cartilage destruction (76%), bone lysis (60%), bone proliferation (40%), and edema of soft tissue (72%).

ig = intragastrical

1.3.2. ANALGESIC EFFECTS (REF. 4, 9, 12, 21)

The analgesic actions of celecoxib (SC-58635) were evaluated in various models and findings are presented in the following table.

Hyperalgesia Models	Species	Dose(mg/kg)/Route	Observations
Carrageenan Induced Hyperalgesia (Hargreave's)	SD rats	3, 10, 30, 50, 100 po	Dose-dependent ↓ with an ED_{50} of 35 mg/kg.
Formalin Model	Swiss-Webster mice	10, 30, 50 po	↓ 67% and 88% at levels of 30 and 50 mg/kg, respectively
Phenyl Benzoquinone (PBQ)-Induced Doxoflexion	Swiss-Webster mice	5 po	↓ 56% of dorsoflexion response
Acetic Acid-Induced Writhing	♂ ICR mice	50, 150 and 500 po	Dose-dependent ↓ the number of dorsoflexions by 54.1, 91.2 and 95.1%, respectively.

1.3.3. ANTIPYRETIC EFFECTS (REF. 7)

The effects of celecoxib on LPS-induced fever were evaluated in rats. Basal body temperature was taken rectally 1 hr prior to ip injection of LPS or saline and then animals were immediately treated intragastrically with 30 mg/kg SC-58635 or 10 mg/kg indomethacin or vehicle immediately post-LPS stimulation. Body temperature was measured at 1 hr intervals for 5 hr post-LPS.
Results showed that oral application of SC-58635 (30 mg/kg) reduced LPS-induced fever in rat by 42% but did not alter normal body temperature.

1.3.4. CHEMOPREVENTION OF AZOXYMETHAN-INDUCED COLONIC ABERRANT CRYPT FOCI (ACF) AND TUMOR (REF. 22, 23)

1.3.4.1. Inhibition of Azoxymethan-Induced Colonic Aberrant Crypt Foci (Ref. 22)

Animals: ♂ F344 rats 5 weeks old

Designs: Groups of rats were fed with either control diet or diet containing SC-58635 (150 or 1500 ppm), Sulindac (320 ppm) or placebo (1500 ppm) for 12 weeks (5-16 weeks of age). Two weeks after placing on diet containing SC-58635, Sulindac or vehicle, all but control rats were given with azoxymethan (AOM), 15 mg/kg, or saline sc 1x/week for 2 weeks. Animals were sacrificed at 16 weeks of age, the colons were removed and fixed in 10% formalin. Microscopic evaluations were performed and ACF were recorded.

Results: Comparable body weights were obtained for each group. No apparent gross pathological changes were noted in the liver, kidney, GI, and lung. The effects of feeding SC-58635 and Sulindac on AOM-induced ACF formation (mean ± SD) are presented in the following table. No evidence of ACF formation in the colon of animals treated with saline was noted.

Treatment Groups (n=12)		AOM-Treatment	Total Nº of ACF/rat	Nº of Foci Containing			
				1 Crypt	2 Crypts	3 Crypts	4 Crypts
Control Diet	-	+	120 ± 15	16 ± 6.5	35 ± 7.7	34 ± 4.6	35 ± 7.9
SC-58635	1500 ppm	+	71 ± 15**	10 ± 4.5*	22 ± 6.8**	20 ± 6.8**	18 ± 5.8**
	150 ppm	+	127 ± 13	16 ± 4.6	44 ± 7.0	35 ± 6.8	33 ± 6.6
Sulindac	320 ppm	+	77 ±14**	11 ± 6.3*	24 ± 8.5**	21 ± 6.6**	21 ± 5.8**
Placebo	1500 ppm	+	111 ± 35	15 ± 7.7	34 ± 11.8	31 ± 10.1	31 ± 10.2

** p≤0.001; * p≤0.05.

1.3.4.2. Inhibition of Azoxymethan-Induced Colonic Tumors (Ref. 23)

Animals: ♂ F344 rats 5 weeks old

Designs: Groups of rats were fed with either control diet or diet containing 1500 ppm of SC-58635 for ≥ 52 weeks. Two weeks after placing on diet containing SC-58635 or control diet, all but control rats were given with azoxymethan (AOM), 15 mg/kg, or saline sc 1x/week for 2 weeks. Body weights were recorded 1x/week for the 1st 8 weeks and 1x/4weeks thereafter. Animals were sacrificed 50 weeks after the second AOM injection. The GIs were removed and tumors (size, location and number) were recorded.

Results: Comparable body weights were obtained for each treatment group. No apparent gross or histopathological changes were noted in the liver, kidney, GI, and lung. The effects of feeding SC-58635 on the incidence of AOM-induced colon tumors, tumor size and tumor volume are shown in the following table. No evidence of colon tumors was noted in animals that were placed on either control or SC-58635 containing diet (9/group) treated with saline.

Treatment	AOM	Type of Tumors		Incidence (%)	Multiplicity (Nº of tumors/rat)	Tumor Size (mm)/ Nº of Tumors		Tumor Volume (mm^3)
Control Diet (N=36)	+	Adenoma		9	0.09 ± 0.28[a]	<5	36	
		Adenocarcinoma	Non-invasive	41	0.59 ± 0.77	5-10	17	
			Invasive	76	1.26 ± 1.01	>10	10	
		Total		85	1.91 ± 1.38			204 ± 483
SC-58635 (1500 ppm) (N=36)	+	Adenoma		0	0	<5	1	
		Adenocarcinoma	Non-invasive	3*	0.03 ± 0.16*	5-10	0	
			Invasive	3**	0.03 ± 0.16**	>10	1	
		Total		6**	0.06 ± 0.23**			27 ± 23

[a] Values expressed as mean ± SD; ** p≤0.000001; * p≤0.001.

1.4. SAFETY PHARMACOLOGY (REF. 5, 18-21, 24-29)

Reports related to safety pharmacology were summarized in the following table.

Study Type	Species	Dose/Route	Results
Effect on General Activity and Behavior			
General Activity and Behavior	Mice, 3/group	0, 50, 150, or 500 mg/kg po	50 & 150 mg/kg: slightly ↓ locomotive activities. 500 mg/kg: ↑ in locomotive activities in ⅓ mice.
Effect on Central Nervous System			
Spontaneous Locomotor Activity	Mice, 10/group	0, 50, 150, or 500 mg/kg po	500 mg/kg: significantly ↓ spontaneous locomotive activities by 87% as compared to control animals at 3 hr post dosing.
Effect on Hexobarbital-Induced Sleep			↑ hexobarbital-induced sleep dose-dependently
Electroshock-Induced Convulsions: Synergestic			≥150 mg/kg: slightly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected.
Electroshock-Induced Convulsions: Antagonistic			↓ incidences of tonic convulsions dose-dependently, the incidences of clonic and mortality were not affected.
Chemical-Induced Convulsions: Synergestic			≥150 mg/kg: significantly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected.
Chemical-Induced Convulsions: Antagonistic			dose-dependently ↓ the incidences of tonic convulsions and mortality, the incidences of clonic were not affected.
Analgesic Activity			Significantly ↓ acetic acid-induced writhing in dose-dependent fashion, but had no effect on tail pinch-induced pain.
Body Temperature	Rat, 8/group	0, 50, 150, or 500 mg/kg po	↔
Effect on Autonomic Nervous System and Smooth Muscle			
Spontaneous Motility	Guinea Pig Isolated Ileum	$4x10^{-8}$ to $4x10^{-5}$ M	$\geq 4x10^{-6}$: significantly ↓ the amplitude of spontaneous motility
Agonist-induced Contraction			$\geq 4x10^{-7}$ M: ↓ $BaCl_2$-induced contractions; $\geq 4x10^{-6}$ M: ↓5-HT-induced contractions; $\geq 4x10^{-5}$ M: ↓ ACh-, Histamine-induced contractions.
Effect on Digestive system	Mice, 10/group	0, 50, 150, or 500 mg/kg po	↔ on the rate passage of charcoal meal in small intestine.
Effect on Respiratory and Cardiovascular Systems	Dog, 3/group	0, 50, 100 or 200 mg/kg	200 mg/kg: ↑ blood flow significantly, ↔ on the ECG, and PR, QT, and QRS interval times, systolic, diastolic, and mean blood pressure, heart rate and respiratory pressure
Effect on Urine Volume, Urinary PGE_2, and Urinary Electrolytes Excretion	Rat, 8/group	0, 50, 150, or 500 mg/kg po	↓ urine volume significantly up to 6 hr postdose, and Na^+, Cl^- excretion; ↑ urinary osmolarity significantly; ↔ on K^+ excretion and pH.
		0, 5, 15, 50, mg/kg po	50 mg/kg: similar effects were obtained as previous test. 15 mg/kg: ↓ urine volume at 3 hr postdose; ↑ urinary osmolarity for 6 hr, excretion of urine electrolytes were not affected.
	♂ Rat, 6/group	600 mg/kg/day x7	↔ urine volume, urinary PGE_2 ↓ kidney PGE_2
	♀ Rat, 8/group	600 mg/kg/day x3 or x7	↔ urine volume, urinary PGE_2

1.5. References

The following pharmacology study reports or published manuscripts were submitted in current NDA.

1.5.1. Evaluation Of Inhibitors Of Cyclooxygenase (COX) Using Human Recombinant COX-1 And COX-2, Document No.: BRD94D1725; Date: 21-May-1995 (Vol. 1.9, p. 1-24)

1.5.2. SC-58635: Inhibition Of Cyclooxygenase 1 And 2 And 5-Lipoxygenase Activities In Human Fibroblasts And In Rodent And Human Whole Blood, Document No.: BRD94D1727; Date: 17-Nov-1994 (Vol. 1.9, p. 25-41)

1.5.3. SC-58635: Inhibition Of Cyclooxygenase 1 And 2 Activities In Human Whole Blood, Document No.: BRD95D1758; Date: 24-May-1995 (Vol. 1.9, p. 42-51)

1.5.4. Evaluation Of The Cyclooxygenase-2 Inhibitor SC-58635 As An Analgesic Agent, Document No.: BRD94D1728; Date: 17-Nov-1994 (Vol. 1.9, p. 52-70)

1.5.5. SC-58635: Pharmacological Inhibition Of Tissue Prostaglandins In Male And Female Rats, Document No.: BRD 95D1755; Date: 18-Apr-1995 (Vol. 1.9, p. 71-96)

1.5.6. SC-58635 And SC-59046: Inhibitory Activity On Cyclooxygenase-2 And Cyclooxygenase-1 In Dog Blood, Document No.: BRD95D1759; Date: 11-May-1995 (Vol. 1.9, p. 97-110)

1.5.7. SC-58635: Pharmacological Inhibition Of Inflammation, Fever And Prostaglandin Production In Rodents, Document No.: BRD94D1726, Date: 28-Nov-1994 (Vol. 1.9, p. 111-134)

1.5.8. Histopathological Evaluation Of Hindlimb Joints From Arthritic Rats Treated With SC-58635, Document No.: PSA95S-30-950031; Date: 11-May-1995 (Vol. 1.9, p. 135-140)

1.5.9. Effect Of Naloxone On The Analgesic Activity Of Cox-2 Inhibitors, Document No.: BRD96D1800; Date: 06-Jun-1996 (Vol. 1.9, p. 141-151)

1.5.10. In Vivo Selectivity Of SC-58635: Pharmacological Inhibition Of Prostaglandin Production In Inflamed Pouch (Cox-2) Vs Stomach (Cox-1) In Rats, Document No.: BRD97D1834; Date: 11-Aug-1997 (Vol. 1.9, p. 152-162)

1.5.11. Mechanism Of Selective Inhibition Of Cox-2 By Celecoxib (SC-58635), Document No.: BRD97D1837; Date: 20-Nov-1997 (Vol. 1.9, p. 163-191)

1.5.12. Modulation Of PGE_2 By Celecoxib In Central Nervous System, Document No.: BRD97D1858; Date: 11-Feb-1998 (Vol. 1.9, p. 192-203)

1.5.13. Crystal Structure Of Cyclooxygenase-2 Complex With SC-58635, Document No.: BRD97D1862; Date: 09-Jan-1998 (Vol. 1.9, p. 204-220)

1.5.14. Comparison Of PGE_2 And Celecoxib Levels In Plasma, Paw Exudate/Synovial Fluid And Cerebrospinal Fluid in Rat Adjuvant Arthritis, Document No.: BRD98D1869; Date: 25-Feb-1998 (Vol. 1.9, p. 221-234)

1.5.15. Lack Of Effect Of Celecoxib On LTB_4 Production In The Reversed Dermal Arthus Reaction, Document No.: BRD98D1870; Date: 17-Feb-1998 (Vol. 1.9, p. 235-244)

1.5.16. Zhang, Y., et al: Inhibition Of Cyclooxygenase-2 Rapidly Reverses Inflammatory Hyperalgesia And Prostaglandin E_2 Production. J. Pharmacol. Exp. Ther. 283(1997):1069-1075. (Vol. 1.9, p. 245-251)

1.5.17. SC-58635: Distribution Into The Central Nervous System (CNS) In The Rat, Document No.: BRD97D1852; Date: 17-Nov-1997 (Vol. 1.9, p. 252-261)

1.5.18. SC-58635: Gastrointestinal Damaging Activity In Rodents, Document No.: BRD94D1723; Date: 06-Oct-1994 (Vol. 1.9, p. 262-276)

1.5.19. Evaluation Of SC-58635 In Panlabs Pharmacology Screen, Document No.: BRD98D1872; Date: 27-Feb-1998 (Vol. 1.9, p. 277-279)

1.5.20. Effect Of SC-58635 On SC-59701 (The Active Moiety Of The Prodrug SC-54684A) And Induced Inhibition Of Platelet Aggregation And Prolongation Of Bleeding Time In Dogs, Document No.: BRD96D1790; Date: 28-Mar-1996 (Vol. 1.9, p. 280-289)

1.5.21. General Pharmacology Study Of SC-58635, Document No.: JBC-95-YXGP-109; Date: 11-Oct-1995 (Vol. 1.9, p. 290-414)

1.5.22. Reddy, B. S. et al: Evaluation Of Cyclooxygenase-2 Inhibitor For Potential Chemopreventive Properties In Colon Carcinogenesis. Cancer Res. 56(1996):4566-4569 (Vol. 1.9, p. 415-418)

1.5.23. Reddy, B. S. et al: Chemopreventive Activity Of Celecoxib, A Specific Cyclooxygenase-2 Inhibitor, Against Colon Carcinogenesis, Cancer Res.58(1998);409-412 (Vol. 1.9, p. 419-422)

1.5.24. Neuropharmacological Profile Of SC-58635 In The Rat, Document No: PSA-94S-4217; Date: 30-Nov-1994 (Vol. 1.51, p. 1-55)

1.5.25. A Pharmacological Assessment Of The Effect Of SC-59046, SC-58553, SC-58635, Or SC-58994 On Renal Function And The Gastrointestinal System Of The Rat When Administered For Four Consecutive Days, Document No.: PSA-94C-4225; Date: 29-Nov-1994 (Vol. 1.51, p. 56-446)

1.5.26. Report Amendment No. 1: A Pharmacological Assessment Of The Effect Of SC-59046, SC-58553, SC-58635 Or SC-58994 On Renal Function And The Gastrointestinal System Of The Rat When Administered For Four Consecutive Days, Document No.: PSA95C-31-EX4225; Date: 05-Sep-1995 (Vol. 1.51, p. 436-446)

1.5.27. Comparison Of Hepatic Activities Of SC-58635, SC-58553, SC-59046 And SC-58994 In Rats, Document No.: PSA-94S-4197; Date: 30-Nov-1994 (Vol. 1.52, p. 1-126)

1.5.28. Cardiopulmonary Assay Of SC-58635 In Guinea Pigs, Document No.: PSA-94C-4229; Date: 29-Nov-1994 (Vol. 1.52, p. 127-186)

1.5.29. Acute Hemodynamic Effects Of The Intravenous Administration Of SC-58635 In Anesthetized Beagle Dogs, Document No.: PSA-94S-4235; Date: 29-Nov-1994 (Vol. 1.53, Vol. 1-39)

1.5.30. Reevaluation Of Histologic Sections Of Kidneys Of Rats, Dogs, And Mouse from Preclinical Safety Studies With Celecoxib (SC-58635); Document No.: P3098002; Date: 5-Mar-1998 (Vol. 1.53, p. 107-140)

2. TOXICOLOGY

2.1. ACUTE (SINGLE DOSE) TOXICITY STUDIES

2.1.1.1. A Single Dose Oral Toxicity Study Of SC-58635 In The Rat Document No.: SBL 77-64; Date:29-Sep-1995 (Vol. 1.10, p. 1-30)

Study Nº:	SBL 77-64
Study Aims:	To determine acute toxicity of SC-58635 in rats.
Compound:	SC-58635 (Lot Nº 94K031-A2A,
Vehicle:	0.5% methylcellulose and 0.1% polysorbate 80 aqueous solution
Dose and Route:	0, 1000, or 2000 mg/kg po by gavage
Animals:	SPF Crj:CD(SD) rats, 5 weeks of age, weighing 131-138 g for ♂ and 117-122 g for ♀, 5/sex/group.
Study Date:	4/26/95 - 9/29/95
Study Site:	
GLP/AUC:	Yes

Study Design: Rats were orally dosed with SC-58635 in 0.5% methylcellulose and 0.1% polysorbate 80 aqueous solution at doses of 0, 1000, or 2000 mg/kg. Animals were monitored for 14 days. The following observations were performed:

- Clinical Signs and Mortality - 2x/day;
- Body Weight- Days 0, 1, 4, 8, and 13;
- Necropsy - Day 14. All organs and tissues were examined macroscopically.
  Histopathology Examination: Histopathology examinations were not performed, as no abnormalities were observed in the gross pathology examination. The liver and kidneys were fixed in 10% neutral buffered formalin and stored.

Results:

- Clinical Signs and Mortality - No deaths occurred. White stool was seen in 4♂ and 5♀ @ 2000 mg/kg on the day of dosing.
- Body Weight - Normal.
- Necropsy - No remarkable abnormalities were seen.

2.1.1.2. A Single Dose Oral Toxicity Study Of SC-58635 In The Dog, Document No.: SBL 77-63; Date:29-Sep-1995 (Vol. 1.10, p. 31-62)

Study Nº:	SBL 77-63
Study Aims:	To determine acute toxicity of SC-58635 in male beagle dogs.
Compound:	SC-58635 (Lot Nº 94K031-A2A,
Vehicle:	Empty gelatin capsule
Dose and Route:	1000 and 2000 mg/kg po
Animals:	♂ beagle dogs, 7-8 month-old, weighing 9.4-10.8 kg, 2/group
Study Date:	4/26/95 - 9/23/95
Study Site:	
GLP/AUC:	Yes

Study Design: ♂ beagle dogs (2/group) were given a single oral dose of SC-58635 in gelatin capsules at doses of 0, 1000, or 2000 mg/kg. Animals were observed for 14 days. The following observation were performed:

- Clinical Signs and Mortality - 2x/day;
- Food Consumption - 1x/day;
- Body Weight - Days 0, 1, 4, 8, and 13;
- Heart Rate & Body Temperature - Days 0, 1, 4, 8, and 13
- Necropsy - Day 14. All organs and tissues were examined macroscopically.
  Organ Weight (absolute and relative): brain (including cerebellum and brain stem), pituitary, thyroids (including parathyroid, weighed after preservation in formalin), submandibular glands, thymus, heart, lungs (including bronchus), liver, adrenals, kidneys, spleen, stomach, testes, epididymides, prostate and urinary bladder
  Histopathology Examination: Histopathology examinations were not performed, as no abnormalities were observed in the gross pathology examination. The heart, spleen, thymus, lungs, bronchus, stomach (fundus, pylorus), small intestine (duodenum, jejunum, ileum), large intestine (cecum, colon, rectum), liver, kidneys and urinary bladder were fixed in 10% neutral buffered formalin and stored.

Results:

- Clinical Signs and Mortality - Vomiting was noted in one each animal at 1000 and 2000 mg/kg immediately after dosing and these dogs had test article like substance in the stool on the day of dosing.
- Food Consumption and Body Weight - Normal.
- Heart Rate and Body Temperature - A slight ↓ in heart rate was noted for 6 hours in one dog @ 2000 mg/kg on Day 0 post dosing.
- Necropsy - No abnormalities were observed.

2.1.1.3. Acute Limits Of Lethality Study Of SC-58635 In The Cynomolgus Monkey, Document No.: PSA95S-30-SA4350; Date: 16-May-1995 (Vol. 1.10, p.63-118)

Study Nº: SA4350
Report Nº: PSA-95S-30-4350
Study Aim: To evaluate the acute lethal dose SC-58635 after single oral administration
Compound: SC-58635 (Lot Nº 94K014-A2B, 100% free compound) suspensions in 0.5% methylcellulose and 0.1% Tween® 80, 10 mg/ml
Dosage & Route: 25 and 250 mg/kg, 5 ml/kg po
Animals: ♀ cynomolgus monkeys, 13 to 15 years of age, weighing 3.48 - 6.014 kg, 3/group
Study Location:
Study Date (In-Life): 2/10/95 - 2/23/95
Compliance with GLP/QAU: Yes
Study Design: Animal grouping and dose allocations are presented in the following table. All animals were monitored for mortality, general appearance and behavior daily. Body weight of each animal was measured on day -1, and day 1 prior to dosing, and on Day 14. Plasma samples were obtained from each animal at 3 and 24 hr after dosing on Day 1 for PK analysis. Necropsies were not performed and all animals were returned to the animal stock pool at the end of experiment.

Group	Treatment	Dose (mg/kg/day)	Nº of Animals
1	SC-58635	25	3 ♀
2	SC-58635	250	3 ♀

Results: No deaths occurred during the experiment; therefore, the LD_{50} of SC-58635 for ♀ cynomolgus monkeys appeared to be >250 mg/kg. Watery stool was observed on Day 1 in one animal from both treatment groups. The one receiving 25 mg/kg/day also showed blood in the stool on Day 2; she appeared to be normal on Days 3-14. Some other animals in either groups had soft or watery stools on Days 7-14. Body weights of all animals were not modified by SC-58635. The mean concentrations of SC-58635 in ♀ cynomolgus monkeys 3 and 24 hr post dosing with 25 and 250 mg/kg/day were presented in the following table.

Treatment Dose (mg/kg/day)	Plasma SC-58635 Levels (μg/ml)	
	3 hr	24 hr
25	0.140 ± 0.016	0.0355 ± 0.0077
250	0.521 ± 0.136	0.144 ± 0.025

2.2. REPEATED DOSE TOXICITY STUDIES

2.2.1. SUBCHRONIC TOXICITY STUDIES

MOUSE STUDIES

2.2.1.1. Two-Week Feasibility Study Of SC-58635 Dietary Admix In The Mouse (EX 4325) Document No.: P30E4325; Date: 17-Sep-1996 (Vol. 1.11, p. 1-315)

Included as an appendix to this report was:
Analysis Of Plasma SC-58635 Concentrations In A Two-Week Feasibility Study Of SC-58635 Dietary Admix In The Mouse, EX4325, Document No.: MRC-95S-0098; Date: 24-May-1995

Report Nº: P30E4325 & MRC-95S-0098 (PK Study)
Study Nº: EX4325
Study Aim: To evaluate the feasibility of dietary admix as a means of SC-58635 dose administration for future long term toxicity studies.
Compound: SC-58635 (Lot Nº 94K014-A4A) mixed with basal diet
Dose & Route: 0, 100, 300, 1000, 3000 mg/kg/day for the toxicology study, and 100, 300 & 1000 mg/kg/day for the companion PK study

Toxicology Study				Satellite PK Study			
Group	Dose (mg/kg/day)	Nº of Animals	Necropsy	Group	Dose(mg/kg/day)	Nº of Animals	Necropsy
1	0	10/sex	10/sex	6	100	15/sex	0/sex
2	100	10/sex	10/sex	7	300	15/sex	0/sex
3	300	10/sex	10/sex	8	1000	15/sex	0/sex
4	1000	10/sex	10/sex				
5	3000	10/sex	10/sex				

Animals: ♂ & ♀ CD-1 Mice, ~6 weeks of age, weighing 28.1-32.2 g for ♂ and 22.0-26.2 g for ♀, 10/sex/group for the toxicology study and 15/group for the PK study
Study Location: G.D. Searle & CO., 4901 Searle Parkway, Skokie, IL 60077
Study Date (In-Life): 01/12/95 - 01/26-27/95
Compliance with GLP/QAU: Not Indicated
Study Design: SC-58635 was given to toxicology study mice in the diet for ≥14 days and PK study mice for ≥13 days. Animals were observed 1x daily for mortality and moribundity. Physical examinations were performed on each animal on Days -7, 1, 7, and 14. Body weights were recorded 2x prior to treatment and 2x/week during treatment. Food consumption was measured for 2 consecutive days before the study and 2x/week during treatment. Serum samples were collected from 5 animals/sex in Groups 1, 2, 3, and 4 for clinical chemistry parameter evaluation on Day 15. Blood was obtained from 5 animals/sex in Groups 1, 2, 3, and 4 for hematology analysis on Day 16. The hematology and clinical chemistry parameters evaluated are listed in the following table.

Scheduled necropsy was performed on Day 15 or Day 16 and microscopic evaluations were performed on specified organs as shown in the following table. For the PK parameter determination, blood samples were collected from 3 animals/sex each in groups 6, 7, and 8 on Days 13 and 14.

HEMATOLOGY		HISTOPATHOLOGICAL EVALUATIONS	
White Blood Cells (WBC)	Mean Corpuscular Volume (MCV)	Brain	Stomach
Differential White Blood Cells	Mean Corpuscular Hemoglobin (MCH)	*Heart	*Testes (Both)
Red Blood Cells	Mean Corpuscular Hemoglobin Concentration (MCHC)	*Kidneys (Both)	*Thymus
Hemoglobin (Hb)	Platelets	*Liver	Intestinal Tract
Hematocrit (Ht)	Mean Platelet Volume	Lung	Gross Lesions

CLINICAL CHEMISTRY				
ALT	Calcium	Globulin	Sodium	Total Protein
Albumin	Chloride	Glucose	Sorbitol Dehydrogenase	Triglycerides
Alkaline Phosphatase	Cholesterol	Inorganic Phosphorus	Total Bile Acids	Urea
AST	Creatinine	Potassium	Total Bilirubin	

* Organs were weighed. Paired organs were weighed together.

Results:

- Dosage Concentration Determination - Dosages were calculated using body weight data, food consumption measurements and dose formulation information, and the actual dosages for each group are given in the following table.

Group	Intended Dose (mg/kg/day)	Actual Dose (mg/kg/day) ♂	Actual Dose (mg/kg/day) ♀
2	100	95 - 102	97 - 106
3	300	275 - 303	301 - 334
4	1000	779 - 1112	925 - 1122
5	3000	1269	2114 - 3000

- Clinical Signs and Survivals - Hunched posture, shivering, reduced activity, higher incidence of ventral staining, and reduce number of feces were major clinical signs seen in SC-58635 treated mice. The mortality or moribundity for each group is shown in the following table.

Group	Dose (mg/kg/day)	Died/Moribund Sacrifice ♂	Died/Moribund Sacrifice ♀
1	0	0/10	0/10
2	100	0/10	0/10
3	300	1/10	0/10
4	1000	2/10	0/10
5	3000	6/10	2/10

- Food Consumption and Body Weight - Significant reductions in mean body weights with reduced food consumption were noted for ♂ @ ≥1000 mg/kg and ♀ @ 3000 mg/kg/day as shown in the following table. Weight loss (negative weight gains) was noted in high dose group.

Parameter	Trt. Day	1000 mg/kg ♂	1000 mg/kg ♀	3000 mg/kg ♂	3000 mg/kg ♀
Mean Body Weight	Day 5	↓4.7%	NS	↓21.7%	↓7.5%
	Days 8-14	↓4.6 - 9%	NS	-	↓9.4%
Mean Food Consumption	Days 1-5	-	↓20%	↓62.3%	↓45.3%
	Days 5-8	↓27.8%	↓14.9%	-	↓38.3
	Days 8-12	↓21.8%	↓8.2%	-	-
	Days 12-14	↓19.2%	↓12.5%	-	-

NS = Non-significant; - = No data available.

- Clinical Pathology - Males @ 1000 mg/kg/days had ↓ (18.4%) serum albumin levels and slightly ↑ ALT values (1.55x). No remarkable findings were observed in hematological analyses.
- Gross Pathology - A slight ↑ (7 to 13%) in liver/body weight ratios was noted in both ♂ & ♀ receiving 1000 mg/kg/day SC58635. Gastrointestinal erosions/ulcers with secondary peritonitis and discolored kidney were major macroscopic changes seen in animals that died or were

sacrificed at moribund. Gross changes found in mice at terminal necropsy were an ulcer in jejunum with fibrinous peritonitis in one ♂ @ 1000 mg/kg and a well demarcated, tan region in the cranial pole of the left kidney in one ♀ @ 1000 mg/kg/day.

- Histopathology - Macro- and micro-scopic examinations were not done on the samples from mice receiving 3000 mg/kg/day. Microscopic lesions found in the mice that died or were sacrificed at moribund included renal papillary necrosis, multiple small foci of transmural necrosis and inflammation with secondary peritonitis and thymic atrophy. Test article-related microscopic changes found in the terminal sacrificed animals (♂ @ ≥300 mg/kg/day and ♀ @ 1000 mg/kg/day) were restricted to the stomach, small and large intestines and kidneys. Pathological changes in the GI were similar to those seen in the mice that died or were sacrificed at moribund. Renal injury with characteristics of focal degeneration of renal tubules with regeneration, epithelial basophilia, intralumental casts (hyaline or cellular) and a minimal mononuclear cell infiltration was seen in 3♂ and 4♀ @ 1000 mg/kg.
- PK - Mean PK parameters for SC58635 on following oral administration to mice via dietary admix for 2-week are presented in the following table. AUC and C_{max} values were higher in **males** than females. A dose proportional increase in AUC and C_{max} values was noted in ♀ @ all dose levels and ♂ @ 100 and 300 mg/kg/day.

Dose (mg/kg/day)	C_{max} (μg/ml)		T_{max} (hr)		AUC_{0-24} (μg•hr/ml)	
	♂	♀	♂	♀	♂	♀
100	3.52	1.52	6	6	55.8	20.4
300	10.4	4.54	6	24	148	60.5
1000	19.7	10.6	6	24	288	162

Based upon the findings of the present study, the NOAEL of SC-58635 in dietary admix was 100 and 300 for ♂ and ♀ mice, respectively. GI (perforated ulcers with secondary peritonitis) and kidney (renal tubule degeneration/regeneration) were the major target organs.

2.2.1.2. Thirteen-Week Range-Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse (EX4357) Document No: P30E4357; Date: 29-Apr-1996 (Vol. 11.17-1.18)

Included as an appendix to this report were:

1. Analysis Of Plasma SC-58635 Concentrations In A Thirteen Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse, EX4537, Document No.: MRC95S-30-950208; Date: 07-Sep-1995
2. Final Report Amendment No. 1: Analysis Of Plasma SC-58635 Concentrations In a Thirteen Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse, EX4357, Document No.: M3195208; Date: 11-Mar-1996
3. Final Report Amendment No. 2: Analysis Of Plasma SC-58635 Concentrations In a Thirteen Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse, EX4357, Document No.: M3295208; Date: 18-Nov-1996
4. Final Report Amendment No. 3: Analysis Of Plasma SC-58635 Concentrations In a Thirteen Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse, EX4357, Document No.: M3395208; Date: 21-Jul-1997
5. Final Report Amendment No. 1: Thirteen-Week Range Finding Dietary Admix Toxicity Study Of SC-58635 In The Mouse (EX4357), Document No.: P31E4357; Date: 14-Oct-1997

Report Nº: P30E4357 & MRC95S-30-950208 (PK Study)
Study Nº: EX4357
Study Aim: To evaluate the toxic effect of SC-58635 in the mouse and to select dosages for a carcinogenicity study in the mouse.
Compound: SC-58635 (Lot Nº 94K014-A3B) mixed with basal diet

Dose & Route: 0, 75, 150 & 300 mg/kg/day for ♂ study, and 0, 150, 300 & 1000 mg/kg/day for the ♀ study.

Animals: ♂ & ♀ CD-1 Mice, ~5 weeks of age, weighing 16.7-33.3 g for ♂ and 19.3-27.7 g for ♀, 20/sex/group for the toxicology study and 90/sex/group for the PK study

Study Location: G.D. Searle & CO., 4901 Searle Parkway, Skokie, IL 60077

Compliance with GLP/QAU: No.

Study Date: 3/28/95 to 6/27-29/95

Study Design: Male and female CD-1 mice were randomly assigned to one of 7 dose groups as shown in the following table.

Toxicology Study Group		PK Study Group		Intended Dose (mg/kg)		Actual Dose (mg/kg)	
Group Nº	Nº of Animals	Group Nº	Nº of Animals	♂	♀	♂	♀
1	20/Sex			0	0	0	0
2	20/Sex	5	90/sex	75	150	70.7 - 78.90	148 - 167
3	20/Sex	6	90/sex	150	300	139 - 163	248 - 329
4	20/Sex	7	90/sex	300	1000	290 - 321	888 - 1103

The following observations were performed.

- Mortality and Clinical Signs - 2x/week day, 1x/weekend day.
- Physical Examination - 1x pretest and 1x/week.
- Body Weight & Food Consumption - 1x/week.
- Hematology & Clinical Chemistry - Week 14; 10 animals/sex from Groups 1-3, and 10 ♂ from Group 4.
- Toxicokinetics - Days 1/2, 45/46, and 87/88.
- Necropsy & Histopathology - Days 92-94. Tissues from Group 4 females were not examined microscopically.

Results:

- Mortality and Clinical Signs - Totals of 18 animals in the Toxicology Study, Groups 1-4, and 29 animals in the PK study, Groups 5-7, were found dead or sacrificed at moribund condition. Mortality data for each group are shown in the following table. Most of the deaths or moribundity were due to SC-58635 treatment related GI toxicity and secondary peritonitis. For the toxicology study animals, the cause of death for one each ♀ at 0, 150 and 1000 mg/kg/day could not be determined and accidental death was found in one ♀ at 0 and 150 mg/kg. As for the PK study animals, death attributable to test article-related GI injury and/or peritonitis was noted for one ♂ @ 75 mg/kg, one ♂ @ 150 mg/kg/day, 5♂ & 1♀ @ 300 mg/kg/day and 15♀ @ 1000 mg/kg/day. Animals at the state of moribund had signs of hunched posture, tremors/shivering, reduced activity, motor incoordination, and cold to touch.

Group	♂		♀	
	Dose (mg/kg/day)	Died/Moribund Sacrifice	Dose (mg/kg/day)	Died/Moribund Sacrifice
1	0	0/20	0	2/20
2	75	0/20	150	2/19
3	150	2/20	300	2/20
4	300	3/20	1000	7/19
5	75	1/60	150	0/60
6	150	2/60	300	1/60
7	300	7/60	1000	18/59

- Body Weight & Food Consumption - Groups 3 and 4 ♀ had significant ↓ (5-10%) in mean body weights and cumulative weight gains starting at Week 5 or Week 6. Females @ 1000 mg/kg/day had a significant reduction in food consumption at Weeks 3, 4, 7, and 11 with values of 85-94% of the control values.

- Hematology & Clinical Chemistry - A dose-dependent ↓ in serum triglycerides was noted in both sexes @ ≥150 mg/kg/day.
- Toxicokinetics - SC-58635 was absorbed systemically following oral dietary administration. It appeared that plasma levels of SC-58635 increased proportionally as the dose increased.

Parameters			Dose Levels (mg/kg)					
			75	150		300		1000
			♂	♂	♀	♂	♀	♀
C_{max} (μg/ml)	Day	1	2.78	6.71	2.99	12.8	6.22	14.6
		45	2.0	4.62	1.92	8.27	2.79	12.8
		87	2.44	3.79	2.04	6.65	3.55	11.5
AUC_{0-24} (μg•hr/ml)	Day	1	38.7	84.7	42.1	216	85.3	226
		45	32.2	70.7	24.2	153	47.0	181
		87	39.6	57.2	30.8	123	48.0	183.0
T_{max} (hr)	Day	1	15	15	12	18	12	6
		45	9.0	9.0	9.0	18	9.0	9.0
		87	12.0	12.0	9.0	9.0	9.0	9.0

- Gross Pathology Histopathological Findings -
  Unscheduled Deaths: The incidence of unscheduled dead (sacrificed moribund or found dead) animals with treatment-related gastrointestinal lesions (perforated ulcers and secondary fibrinous peritonitis) is shown in the following table.

Group	♂ Died/Moribund Sacrifice		♀ Died/Moribund Sacrifice	
	Dose (mg/kg/day)	GI Lesions	Dose (mg/kg/day)	GI Lesions
1	0	0/20	0	0/20
2	75	0/20	150	0/19
3	150	2/20	300	2/20
4	300	3/20	1000	7/19
5	75	1/60	150	0/60
6	150	1/60	300	1/60
7	300	5/60	1000	15/59

Terminal Sacrifice: Treatment-related macro- and micro-scopic findings were restricted to the GI tract. In the gross examination, gastrointestinal hemorrhage or mucosal injury were noted in 2/18 ♂ @ 150 and 1/17♂ @ 300 mg/kg/day and black GI contents suggestive of intralummental hemorrhage were observed in 1♀ @ 300 mg/kg. Microscopic lesions including ulceration of the stomach and ileum, inflammation of gastric submucosa, transmural inflammation of the stomach and jejunum, and secondary peritonitis were identified in 1/20 ♂ @ 75, 2/18 ♂ @ 150, and 4/17 ♂ and 1/19 ♀ @ 300 mg/kg/day. A slight → mild nephropathy with characteristics of focal loss of tubule with tubular regeneration, occasional hyaline or cellular cast, and slight to mild mononuclear cell interstitial infiltration were noted in all groups of animals.

Therefore, the NOAEL for ♀ mice was 150 mg/kg/day. The NOAEL was not established for ♂ mice. GI (perforated ulcers with secondary peritonitis) was the major target organ. Inconclusive nephropathy was noted.

RAT STUDIES

2.2.1.3. Range-Finding Toxicity Study (Escalating Dose Design) with SC-58635, SC-58553, SC-59046 And SC-58994 In Rats, Document No.: PSA95S-30-EX4219; Date: 20-Mar-1995 (Vol. 1.12, p. 1-335)

Included as an appendix to this report was:
Plasma Concentration Data From The 15-Day Escalating Dose Toxicity Study Of SC-58635 In The Rat, EX4219, Document No.: MRC-94S-0207; Date: 13-Feb-1995