

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20998/S007

PHARMACOLOGY REVIEW(S)

NDA # 21-156

Division of Oncology Drug Products, HFD-150
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review No. 1

Keywords: chemoprevention, supplemental NDA

NDA No.: 21-156

Serial No(s): 003 **Type:** NDA **Letter dated:** 6/24/99 **Received by CDR:** 6/29/99

Information to be Conveyed to Sponsor: Yes (), No (X)

Reviewer: Wendelyn J. Schmidt, Ph.D.

Review Completion Date: 10/19/99

Sponsor: G.D. Searle

Drug:

Code Name: SC-58635

Generic Name: celecoxib

Trade Name: Celebrex

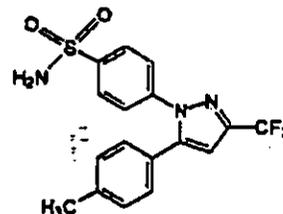
Secondary therapy(s): none

Chemical Name: 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

CAS Registry Number:

Molecular formula/weight: C₁₇H₁₄F₃N₃O₂S, mw=381.38

Structure:



Related INDs/NDAs/DMFs: NDA 20-998, IND

Drug Class: NSAID

Indication: "for the regression and prevention of adenomatous colorectal polyps which may lead to the development of colorectal cancer in patients with familial adenomatous polyposis."

Clinical Formulation: 200 mg capsules Inactive ingredients; croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate and titanium dioxide.

Route of Administration and dosage form: oral

Proposed Dose and Schedule: 400 mg BID in familial adenomatous polyposis

Previous Review(s), Date(s) and Reviewer(s): NDA 20-998: Dr. Josie Yang, 1998; IND W. Schmidt 12/96 and 3/97.

Studies Reviewed within this submission:**Pharmacodynamics**

1. Chemoprevention studies using celecoxib in the Min Apc mutant mouse model of adenomatous polyposis Vol: 1.2 pg 19.
2. Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, against UV-induced skin carcinogenesis. Vol. 1.2 p 38.

Pharmacokinetics

1. Pharmacokinetics of celecoxib in discovery animal models for chemoprevention. Vol 1.2 pg 68.

Studies Not Reviewed within this submission:

1. Arber, N. et al., 1997. A K-ras oncogene increases resistance to sulindac-induced apoptosis in rat enterocytes. *Gastroenterology* 113(6): 1892-1900.
2. Battu, S. 1998. Cyclooxygenase-2 expression in human adenocarcinoma cell line HT29 cl. 19A. *Anticancer Res.* 18: 2397-2404.
3. Beazer-Barclay, Y et al., 1996. Sulindac suppresses tumorigenesis in the Min mouse. *Carcinogenesis* 17(8): 1757-1760.
4. Bishop, PR et al., 1994. Inhibition of immediate early gene expression by sulindac sulfide in rat intestinal epithelial cells. *Gastroenterology* 106: A372. ABSTRACT.
5. Boolbol, SK et al., 1998. COX-2 overexpression and tumor formation are blocked by sulindac in a murine model of familial adenomatous polyposis. *Cancer Res.* 56: 2556-2560.
6. Buckman, S et al., 1998. COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer. *Carcinogenesis* 19(5): 723-729.
7. Chan, TA et al., 1998. Mechanism underlying non-steroidal antiinflammatory drug-mediated apoptosis. *PNAS* 95: 681-686.
8. Chinery, R et al., 1998. Antioxidants reduce COX-2 expression, prostaglandin production and proliferation in colorectal cancer cells. *Cancer Res.* 58: 2323-2327.
9. Dannenberg, AJ et al., 1996. COX-2 is up regulated in transformed mammary epithelial cells. *Proc AACR* 37: 146. ABSTRACT
10. DuBois, RN et al., 1996. Increase COX-2 levels in carcinogen-induced rat colonic tumors. *Gastroenterology* 110: 1259-1262.
11. Elder, DJE et al., 1997. NSAIDs to prevent colorectal cancer: a question of sensitivity. *Gastroenterology* 113: 1999-2008.
12. Elder, DJE et al., 1997. Induction of apoptotic cell death in human colorectal carcinoma cell lines by a COX-2 selective nonsteroidal anti-inflammatory drug: independence from COX-2 protein expression. *Clin. Cancer Res.* 3L 1679-1683.
13. Fischer, SM et al., Chemopreventive activity of celecoxib, a specific COX-2 inhibitor, against UV-induced skin carcinogenesis. In press.
14. Hara, A et al., 1997. Apoptosis induced by NS-398, a selective COX-2 inhibitor, in human colorectal cancer cell lines. *Jpn. J. Cancer Res.* 88: 600-604.
15. Hecht, JR et al., 1995. COX-2 expression and regulation in colonic mucosa, cancer and cell lines. *Proc AACR* 36: 598. ABSTRACT.
16. Hong, WK et al., 1997. Recent advances in chemoprevention of cancer. *Science* 278: 1073-1077.
17. Hwang, D et al., 1998. Expression of COX-1 and COX-2 in human breast cancer. *JNCI* 90(6): 455-460.
18. Jacoby, RF et al., 1996. Chemoprevention of spontaneous intestinal adenomas in the Apc^{min} mouse model by the nonsteroidal anti-inflammatory drug piroxicam. *Cancer Res.* 56:

19. Jalbert, G et al., 1992. Effects of NSAIDs on NNK-induced pulmonary and gastric tumorigenesis in A/J mice. *Cancer Letters* 66: 21-28.
20. Kawamori, T et al., 1998. Chemopreventive activity of celecoxib, a specific COX-2 inhibitor, against colon carcinogenesis. *Cancer Res.* 58: 409-412.
21. Kelloff GJ et al., 1995. Approaches to the development and marketing approval of drugs that prevent cancer. *Cancer Epidemiology, Biomarkers and Prevention* 4: 1-10.
22. Liu, X-H et al., 1997. Involvement of protein kinase C in COX-2 expression, activation and subcellular translocation in a human breast cancer cell line. *Proc AACR* 38: 620. ABSTRACT.
23. Morin, PJ et al., 1997. The gatekeeper has many keys: dissecting the function of the APC gene. *Gastroenterology* 113:2009-2012.
24. Oshima, M et al., 1996. Suppression of intestinal polyposis in APC^{Δ716} knockout mice by inhibition of COX-2. *Cell* 87: 803-809.
25. Parrett, ML et al., 1997. COX-2 gene expression in human breast cancer. *Int. J. Oncol.* 10:503-507.
26. Pentland, AP et al., 1997. Induction of COX-2 by UVB: potential role in the development of human skin cancer. *J. Invest. Derm* 108: 547. ABSTRACT
27. Piazza, GA et al., 1997. Sulindac sulfone inhibits azoxymethane-induced colon carcinogenesis in rats without reducing prostaglandin levels. *Cancer Res.* 57: 2909-2915.
28. Piazza, GA et al., 1996. Induction of apoptosis by sulindac metabolites involves a p53 and bcl-2 independent mechanism and does not require cell cycle arrest. *Gastroenterology* 111): 577A. ABSTRACT.
29. Reddy, BS et al., 1996. Evaluation of COX-2 inhibitor for potential chemopreventive properties in colon carcinogenesis. *Cancer Res.* 56: 4566-4569.
30. Reddy, BS et al., 1993. Inhibitory effect of aspirin on azoxymethane-induced colon carcinogenesis in F344 rats. *Carcinogenesis* 14(8): 1493-1497.
31. Ristimaki, A et al., 1997. Expression of COX-2 in human gastric carcinoma. *Cancer Res.* 57: 1276-1280.
32. Sano, H et al., 1995. Expression of COX-1 and COX-2 in human colorectal cancer. *Cancer Res.* 55: 3785-3789.
33. Seibert, K et al., 1994. Pharmacological and biochemical demonstration of the role of COX-2 in inflammation and pain. *PNAS* 91: 12013-12017.
34. Sheng, GG et al., 1997. A selective COX-2 inhibitor suppresses the growth of H-ras transformed rat intestinal epithelial cells. *Gastroenterology* 113: 1883-1891.
35. Sheng, H et al., 1997. Inhibition of human colon cancer cell growth by selective inhibition of COX-2. *J. Clin. Invest.* 99(9): 2254-2259.
36. Shiff, SJ et al., 1997. Nonsteroidal anti-inflammatory drugs and colorectal cancer: evolving concepts of their chemopreventive actions. *Gastroenterology* 113: 1992-1998.
37. Subbaramaiah, K et al., 1996. Transcription of COX-2 is enhanced in transformed mammary epithelial cells. *Cancer Res.* 56: 4424-4429.
38. Subbaramaiah, K et al., 1997. Inhibition of cyclooxygenase: a novel approach to cancer prevention. *PSEBM* 216: 201-210.
39. Tjandrawinata, RR et al., 1997. Induction of COX-2 mRNA by prostaglandin E2 in human prostatic carcinoma cells. *Br. J. Cancer* 75(8): 1111-1118.
40. Tsuji, S et al., 1996. Evidences for involvement of COX-2 in proliferation of two gastrointestinal cancer cell lines. *Prostaglandins, leukotrienes, and essential fatty acids* 55(3): 179-183.
41. Tsujii, M et al., 1998. Cyclooxygenase regulates angiogenesis induced by colon cancer

cells. *Cell* 93: 705-716.

42. van Ryn, J et al., 1997. Selective COX-2 inhibitors: pharmacology, clinical effects and therapeutic potential. *Exp. Opin. Invest. Drugs* 6(5): 609-614.

43. Watson, AJM. 1998. Chemopreventive effects of NSAIDs against colorectal cancer: regulation of apoptosis and mitosis by COX-1 and COX-2. *Histol. Histopathol.* 13: 591-597.

44. Wilson, KT et al., 1998. Increased expression of inducible nitric oxide synthase and COX-2 in Barrett's esophagus and associated adenocarcinomas. *Cancer Res.* 58: 2929-2934.

Studies Previously Reviewed:

IND _____ by W. Schmidt

1. Marnett, LJ. Aspirin and the potential role of prostaglandins in colon cancer. *Cancer Res.* 52: 5575-5589. 1992.
2. Thun, MJ. et al. Aspirin use and reduced risk of fatal colon cancer. *NEJM* 325: 1593-1596. 1991.
3. Peleg, Il et al. Aspirin and nonsteroidal anti-inflammatory drug use and the risk of subsequent colorectal cancer. *Arch. Intern. Med.* 154: 394-399. 1994.
4. Logan, RFA et al. Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: case-control study of subjects participating in the Nottingham fecal occult blood screening programme. *Br. Med. J.* 307: 285-289, 1993.
5. Martinez, ME et al. Aspirin and other nonsteroidal anti-inflammatory drugs and risk of colorectal adenomatous polyps among endoscoped individuals. *Cancer Epidemiol. Biomarkers Prev.* 4: 703-7070, 1995.
6. Schreinemachers, DM and RB Everson. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. *Epidemiology* 5: 138-146, 1994. ABSTRACT
7. Giovannucci, E et al. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. *Ann. Intern. Med.* 121: 241-246, 1994.
8. Thun MJ et al. Aspirin use and risk of fatal cancer. *Cancer Res.* 53: 1322-1327. 1993.
9. Nugent, KP et al. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br. J. Surg.* 80: 1618-1619. 1993.
10. Winde, G. et al. Complete reversion and prevention of rectal adenomas in colectomized patients with familial adenomatous polyposis by rectal low-dose sulindac maintenance treatment. *Dis. Colon Rectum.* 38: 813-830. 1995.
11. Spagnesi MT et al. Rectal proliferation and polyp occurrence in patients with familial adenomatous polyposis after sulindac treatment. *Gastroenterology* 106: 362-366. 1994.
12. Waddell, WR et al. Sulindac for polyposis of the colon. *Am. J. Surg.* 175-179. 1989.
13. Giardiello, FM et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyps. *NEJM* 328: 1313-1316. 1993.
14. Labayle, D. et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology* 101: 635-639. 1991.
15. Pasricha, PJ et al. The effects of sulindac on colorectal proliferation and apoptosis in familial adenomatous polyposis. *Gastroenterology* 109: 994-998. 1995.
16. Giardiello, Fm et al. Sulindac induced regression of colorectal adenomas in familial adenomatous polyposis: evaluation of predictive factors. *Gut* 38: 578-581. 1996.
17. Rigau, J et al. Effects of long-term sulindac therapy on colonic polyposis. *Ann Intern. Med.* 115: 952-954, 1991.
18. Lynch, HT et al. Rectal cancer after prolonged sulindac chemoprevention. *Cancer* 75: 936-938. 1995.

19. Reddy, BS. et al. Aspirin inhibits colon carcinogenesis in F344 rats. Proc. Ann. Meet. Am Assoc Cancer Res. 34: 557 abstract # 3319. 1993.
20. Pence, DC et al. Experimental chemoprevention of colon carcinogenesis by combined calcium and aspirin. Proc. Ann. Meet Am. Assoc. Cancer Res. 35: 624 abstract # 3719. 1994.
21. Pereira, MA et al. Piroxicam-induced regression of AOM-induced aberrant crypt foci and prevention of colon cancer in rats. Carcinogenesis 17:373-376. 1996.
22. Reddy, BS et al. Inhibition of colon carcinogenesis by prostaglandin synthesis inhibitors and related compounds. Carcinogenesis 13: 1019-1023, 1992.
23. Skinner, SA et al. Sulindac inhibits the rate of growth and appearance of colon tumors in the rat. Arch. Surg. 126: 1094-1096. 1991.
24. Pollard, M et al. Effect of indomethacin on intestinal tumors induced in rats by the acetate derivative of dimethylnitrosamine. Science 214: 558-559. 1981.
25. Narisawa, T. et al. Inhibition of development of methylnitrosourea-induced rat colon tumors by indomethacin treatment. Cancer Res. 41: 1954-1957. 1981.
26. Moorghen, M et al. A protective effect of sulindac against chemically induced primary colonic tumors in mice. J. Pathol. 156: 341-347. 1988.
27. Jacoby, RF. et al. Chemoprevention of spontaneous intestinal adenomas in the Apc min mouse model by the nonsteroidal anti-inflammatory drug piroxicam. Cancer Res. 56: 710-714, 1996.
28. Beazer-Barclay, Y. et al. Sulindac suppresses tumorigenesis in the min mouse. Carcinogenesis 17: 1757-1760. 1996.
29. Boolbol, SK et al. COX-2 overexpression and tumor formation are blocked by sulindac in a murine model of familial adenomatous polyposis. Cancer Res. 56: 2556-2560. 1996.
30. Takahashi, M. et al. Suppression of AOM-induced aberrant crypt foci in rat colon by nimesulide, a selective inhibitor of cyclooxygenase-2. J. Cancer Res. Clin. Oncol. 122: 219-222, 1996.
31. Reddy, BS et al. Evaluation of cyclooxygenase-2 inhibitor for potential chemopreventive properties in colon carcinogenesis. Cancer Res. 56: 4566-4569. 1996.
32. Waddell, WR et al. Adenomatous polyposis coli, protein kinases, protein tyrosine phosphatase: the effect of sulindac. J. Surg. Oncol. 58: 252-256, 1995.
33. Rigas, B et al. Altered eicosanoid levels in human colon cancer. J. Lab. Clin. Med. 122: 518-523. 1993.
34. Eberhart, CE et al. Up-regulation of COX-2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology 107: 1183-1188, 1994.
35. Kargman, SI et al. Expression of prostaglandin G/H synthase-1 and -2 protein in human colon cancer. Cancer Res. 55: 2556-2559. 1995.
36. Gustafson-Svard, C. et al. COX-1 and COX-2 gene expression in human colorectal adenocarcinomas and in AOM induced colonic tumors in rats. Gut 38: 79-84. 1996.
37. DuBois, RN et al. Increased COX-2 levels in carcinogen induced rat colonic tumors. Gastroenterology 110: 1259-1262. 1996.
38. Alberts, DS et al. Do NSAIDS exert their colon cancer chemoprevention activities through the inhibition of mucosal prostaglandin synthetase? J. Cell Biochem. 22: 18-23, 1995.
39. Thompson, et al. Inhibition of mammary carcinogenesis in rats by sulfone metabolite of sulindac. JNCI 87: 1259-1260, 1995.
40. Bedi et al. Inhibition of apoptosis during development of colorectal cancer. Cancer Res. 55: 1811-1816, 1995.
41. Giovannucci, E et al. Aspirin and the risk of colorectal cancer in women. NEJ Med. 333: 609-614, 1995.

42. Earnest, DL et al. Inhibition of prostaglandin synthesis: potential for chemoprevention of human colon cancer. *Cancer Bull.* 43: 561-568, 1991.

IND

1. 26 week repeated dose oral gavage toxicity study in rats with SC-58395 (SA4366); Document # P3OS4366 dated 16 Sept 1996. (vol 29.2-29.4)
2. Evaluation of total Radioactivity Data in a pharmacokinetics and metabolism study of 14C-SC58635 after oral administration to humans. (vol. 29.2)

IND

1. 52 week capsule toxicity study with SC-58635 in dog (SA4425) (26 week interim evaluation); Document number P3IS4425 dated 23 Sept 1996.
See also J. Yang review for NDA 20-998

Note: Portions of this review were excerpted directly from the sponsor's submission.

INTRODUCTION and DRUG HISTORY:

Celecoxib was approved in 1998 for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis in adults. The pharmacodynamics (inhibition of COX-2), pharmacokinetics, and toxicology (including genetic and reproductive toxicology) were reviewed by Dr. Josie Yang for that NDA. The drug is not recommended for use in late pregnancy as it may result in premature closure of the ductus arteriosus.

PREVIOUS CLINICAL EXPERIENCE:

Celecoxib has been used to treat osteoarthritis and rheumatoid arthritis at 100 mg bid or 200 mg bid or qd for up to 12 weeks. A lower incidence of gastrointestinal ulceration (as seen with naproxen), a slight chance of liver enzyme elevation, a possibility of renal effects, and a low incidence of anemia have been observed with celecoxib.

PHARMACOLOGY:Mechanism of action:Drug Activity related to proposed indication

1. Chemoprevention studies using celecoxib in the Min APC mutant mouse model of adenomatous polyposis Vol. 1.2 pg 19.

Species used: heterozygous (genotyped) C57BL/6J (*Min/+*) mice, 30 days old, n=12

Drug dose/schedule: Daily for up to 6 weeks (either age 30-80 days or age 55-80 days) as dietary admix at 0, 150, 500 or 1500 ppm (approximately 0, 22, 75, and 225 mg/kg/day or 0, 66, 225, and 675 mg/m²/day). Positive controls of piroxicam treated mice (50 ppm or 7.5 mg/kg/day) were also used.

Observations: colon and small intestinal tumors (#, size, location) thromboxane B₂ levels, body weight, and plasma celecoxib levels (timing unspecified).

Results: The authors stated that most tumors in Min mice appear by day 55. Body weights did not differ to a biologically relevant extent in treated vs. controls, including the piroxicam group. The timing of the plasma drug levels was not specified; however, despite broad variability, approximately 1.8 ug/mL and 0.7 ug/mL celecoxib were measured in the age 30-80 and 55-80 days groups "near the end of the experiment". The tumor multiplicity and size data are shown in the following tables.

The lack of effect on body weight suggests that the dose selection was appropriate (>10% decrement in body weight by itself can decrease the number of tumors in most models). Later treatment (treatment on days 55-80) was slightly less effective in decreasing the number

Min/Apc Mice Treated with Celecoxib or Piroxicam from age 55-80 days

n = 12 mice per group

Treatment in diet	Small intestine tumor multiplicity			colon tumor multiplicity	total tumor multiplicity	% control
	proximal	mid	distal			
control	4.8 ± 1.8	8.9 ± 4.3	8.3 ± 3.2	.83 ± 1.1	22.9 ± 6.8	100
Celecoxib 150 ppm	4.4 ± 1.8	6.9 ± 4.4	5.9 ± 3.0	.75 ± 1.4	18.0 ± 7.8	79
Celecoxib 500 ppm	5.1 ± 2.4	8.2 ± 3.7	4.6 ± 2.4	.42 ± .67	16.3 ± 6.2	71
Celecoxib 1500 ppm	2.2 ± 1.5	4.1 ± 3.9	2.8 ± 1.7	2.1 ± 1.8	11.1 ± 6.8	48
Piroxicam 50 ppm	3.7 ± 3.6	1.9 ± 1.6	1.1 ± .79	1.4 ± 1.2	7.9 ± 4.8	34

Min/Apc Mice Treated with Celecoxib or Piroxicam from age 30-80 days

n = 12 mice per group

Treatment in diet	Small intestine tumor multiplicity			colon tumor multiplicity	total tumor multiplicity	% control
	proximal	mid	distal			
control	4.7 ± 2.5	9.0 ± 4.4	7.3 ± 3.5	1.5 ± 1.8	22.4 ± 9.0	100
Celecoxib 150 ppm	2.8 ± 2.3	5.8 ± 4.7	6.8 ± 3.9	0.8 ± 1.0	15.8 ± 9.5	71
Celecoxib 500 ppm	4.8 ± 2.3	4.3 ± 2.5	8.2 ± 2.8	0.5 ± 0.7	15.8 ± 4.8	71
Celecoxib 1500 ppm	2.5 ± 1.4	1.8 ± 2.1	1.8 ± 1.8	0.6 ± 0.7	6.5 ± 4.2	29
Piroxicam 50 ppm	2.9 ± 3.1	0.9 ± 0.9	0.8 ± 1.0	0.8 ± 0.7	5.2 ± 4.0	23

Min/Apc Mice Treated with Celecoxib from age 55-80 days

n = 12 mice per group

Treatment in diet	Small intestine tumor diameters			colon tumor diameters
	proximal	mid	distal	
control	3.8 ± 1.8	2.4 ± 0.9	1.9 ± 0.5	5.9 ± 1.9
Celecoxib 150 ppm	3.4 ± 1.4	2.2 ± 0.8	1.7 ± 0.5	5.5 ± 1.8
Celecoxib 500 ppm	3.0 ± 1.2	2.0 ± 0.6	1.5 ± 0.3	5.9 ± 0.9
Celecoxib 1500 ppm	3.4 ± 2.0	1.8 ± 0.6	1.5 ± 0.6	4.9 ± 1.6

Min/Apc Mice Treated with Celecoxib from age 30-80 days

n = 12 mice per group

Treatment in diet	Small intestine tumor diameters			colon tumor diameters
	proximal	mid	distal	
control	3.4 ± 1.4	2.5 ± 0.9	1.7 ± 0.6	5.3 ± 1.8
Celecoxib 150 ppm	2.7 ± 1.3	1.9 ± 0.7	1.6 ± 0.5	5.5 ± 1.4
Celecoxib 500 ppm	2.3 ± 0.9	1.7 ± 0.6	1.4 ± 0.5	3.9 ± 1.6
Celecoxib 1500 ppm	2.3 ± 1.0	1.8 ± 0.5	1.2 ± 0.4	3.9 ± 1.4

and size of tumors than treatment from day 30-80. There were no statistical differences in colon tumor multiplicity with celecoxib dose (large experimental error). A dose response in small intestinal tumor multiplicity with both treatment schedules was observed. Tumor cell multiplicity in the HD celecoxib (1500 ppm) and the piroxicam (50 ppm) groups did not differ to a statistically significant extent. There was no remarkable effect on tumor size with either NSAID treatment. No effects on thromboxane levels with either celecoxib or piroxicam treatment was observed, partly due to wide errors.

2. Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, against UV-induced skin carcinogenesis. Vol. 1.2 p 38.

Species used: HR-1hrBr hairless mice, 8 weeks old, n=30/group

Drug: celecoxib (0, 150, 500, 1500 ppm or approximately 22.5, 75, 225 mg/kg) or indomethacin (4 ppm 0.6 mg/kg) as dietary admix beginning 1 week prior to UV, UV irradiation @ 90-275 mJ/cm² 3X/wk for 9 weeks.

Duration of experiment; 25 weeks

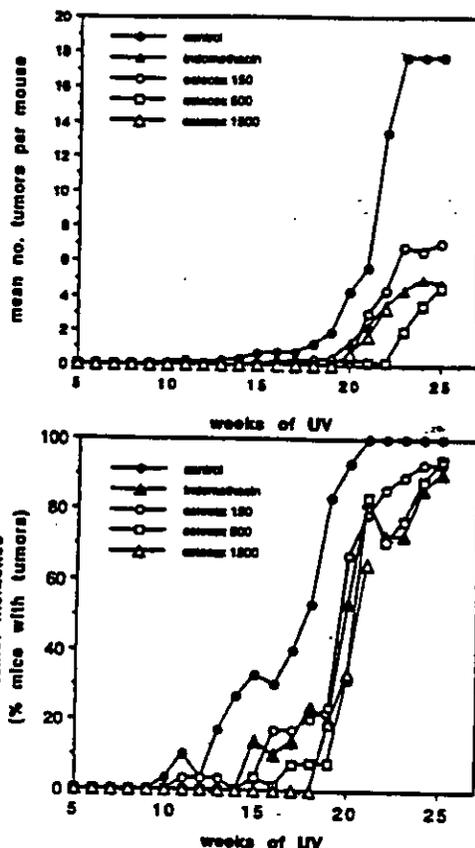
Observations: food consumption, body weight (weekly), at sacrifice: # mice w/ tumors, # tumors/mouse, tumor histology, tumor RNA (COX-1,2 expression), BrdU positive cells, vascular permeability, PGE₂ levels.

Results:

No animals in the control group died prior to scheduled sacrifice (no specific mention was made of deaths in the LD, MD celecoxib groups or the indomethacin group). Beginning at week 4, at least 1 mouse/week died for the remainder of the study. The animals in the HD group weighed between 10 and 20% less than the control mice beginning by week 6. No concurrent drop in food consumption was seen.

Tumors were first noted in the control group at week 10. Tumors were first noted in the 1500 ppm celecoxib group at week 19. At 20 weeks, all of the control mice had tumors while approximately 80% of the NSAID treated mice had tumors, and at 23 weeks approximately 90% of the NSAID treated mice had tumors. No dose response was observed. The number of tumors/mouse was significantly diminished (approximately 1/3 as many tumors) with NSAID treatment at weeks 20-23. Dose minimally affected tumor multiplicity. NSAIDs had no effect on BrdU labeling index or degree of edema, with the exception of the 1500 ppm celecoxib, which increased edema by approximately 40%. PGE₂ levels were decreased to less than 1/3 of the control in NSAID treated animals. The difference between PGE₂ levels with 500 and 1500 ppm celecoxib were minimal.

It should be noted that figures 5, 6, and 7 were not included, which includes the discussion of the COX-2 mRNA and enzyme levels. The author described no effects of the celecoxib or indomethacin on these parameters. The pharmacokinetics from this experiment are described in the PK section.



SAFETY PHARMACOLOGY

PHARMACOKINETICS AND TOXICOKINETICS:

1. Pharmacokinetics of celecoxib in discovery animal models for chemoprevention. Vol 1.2 pg 68.

Blood samples from the efficacy experiments reviewed above were analyzed by for celecoxib. The data is presented below. The plasma concentration levels are difficult to relate to the human levels, as the animal data is based on ad libitum feeding vs. "gavage" in humans. However, as a rough approximation, C_{max} in humans after a 200 mg dose (3.33 mg/kg or 123 mg/m²) was 705 ng/mL, approximately 5 fold less than the plasma levels seen in the HD celecoxib AOM model. C_{max} levels in the human at 200 mg were only slightly below the LD plasma levels, where significant decrements in small intestine and colon tumor numbers were observed with long term treatment. Mean plasma levels in the two experiments at 150 ppm were remarkably similar; mean plasma levels at 1500 and 500 ppm also showed great similarity. Prior data in the rat (NDA 20-998) suggested the beginning of a plateau for C_{max} between 400 and 600 mg/kg.

Plasma Concentrations of Celecoxib in the Rat AOM Model of Chemoprevention Pharmacokinetics Parameters of Celecoxib in the Mouse UV Skin Tumor Model

Time	Plasma Celecoxib (µg/mL) at 150 ppm	Plasma Celecoxib (µg/mL) at 1500 ppm
At Sacrifice*	0.885	3.73
At Sacrifice*	1.41	3.65
At Sacrifice*	0.576	3.30

* Blood samples were collected at sacrifice following 11 weeks of dosing

Dose (ppm)	AUC _{0-24hr} (µg/ml/hr)	T _{max} (hours)	C _{max} (µg/ml)
150	20.5	15	1.81
500	79.0	15	4.66

* Pharmacokinetic parameters were determined after 4 weeks of dosing.

Plasma Concentrations of Celecoxib in the Mouse UV Skin Tumor Model

Time of Day	Plasma Celecoxib (µg/mL) at 150 ppm	Plasma Celecoxib (µg/mL) at 500 ppm
12 pm	0.214	3.34
6 pm	1.07	1.19
12 am	0.637	4.36
3 am	1.61	4.66
6 am	1.13	4.05

* Blood samples were collected following 4 weeks of dosing.

OVERALL SUMMARY AND EVALUATION:

The use of NSAIDs has been associated with decreased incidence of colon cancer in epidemiologic studies. In addition, animal models have been used to investigate the effects of NSAIDs and specific COX-2 inhibitors (like celecoxib) on the progression, incidence and multiplicity of various tumor types, particularly focusing on colon carcinogenesis. Both *in vitro* and *in vivo* studies have associated overexpression of COX-2 with neoplastic areas, increased prostaglandins, and decreased apoptosis.

Two major types of models are used to investigate the prevention of the carcinogenic process: chemical induction of tumor formation (e.g. AOM induction of colon adenocarcinoma in the rat), and mutant strains with early onset/higher incidence of tumors (e.g. the APC Min mutant mouse). Endpoints are usually tumor incidence and multiplicity, although biomarkers, such as aberrant crypt foci (ACF) have also been used. Doses of celecoxib for 9 weeks in the diet at 67 and 70 mg/kg/day in the AOM model resulted in a 40% reduction in incidence in ACFs (Reddy et al., Cancer Res. 56: 4566-4569, 1996). In the Min APC model (discussed above), the number of tumors in the colon was reduced by approximately half with administration of 225 mg/kg/day celecoxib if treatment was started by age 55 days, while greater reductions in tumor #/mouse were seen with earlier intervention. Size of tumors were minimally affected by celecoxib. In an UV induced skin tumor model, overall incidence of tumors was minimally affected, while # of tumors/mouse was decreased by >75% as compared to controls with 225 mg/kg/day celecoxib. Human plasma levels of celecoxib following a dose of 200 mg were similar to plasma levels at the lowest dose used in the AOM model of tumor formation. Significant decrements in tumor multiplicity were also observed at the LD.

The toxicologic testing of celecoxib was extensive and appropriate for a chemopreventive agent. Toxicity studies of 6 months duration in the rodent (rat) and 1 year duration in the non-rodent (dog) were conducted. The 2 year bioassay for carcinogenicity was conducted in both rats and mice and celecoxib was deemed non-carcinogenic. Similarly, celecoxib was not mutagenic or clastogenic in the Ames, CHO mutation or chromosomal aberration, or rat micronucleus studies. Celecoxib did not impair fertility in either sex, and was not teratogenic in rabbits. A series of fetal variations were observed in rats and rabbits and are described extensively in the Pregnancy section of the label.

RECOMMENDATION: The pharmacology/toxicology data supports approval of celecoxib for the supplementary indication in FAP patients. No changes in pharmacology/toxicology sections of the label were proposed and the label is acceptable as written.

- a) Comments for further studies: none
- b) Points discussed with Medical Officer: none

Draft Letter to the Sponsor: n/a

/ S /

Wendelyn J. Schmidt, Ph.D.
Pharmacologist/Toxicologist

 11/14/99
Date

Concurrence: / S /
Paul A. Andrews, Ph.D.
Pharmacology Team Leader

 11/18/99
Date

Original IND/NDA/DMF
c.c. /Division File
 /WSchmidt
 /PAAndrews
 /JChiao
 /PZimmerman