CHAPTER II

LITERATURE REVIEW

This chapter comprised an overview of COX inhibitors, efficacy of specific COX II inhibitors, adverse effect of specific COX II inhibitors, pharmacoeconomic evaluation of specific COX II inhibitors and high risk of gastrointestinal complications. The detail was described in the following:

Overview of COX Inhibitors

1.1 Classification of COX Inhibitors

Cyclooxygenase inhibitors can be classified into four groups as follows (8,9)

1.1.1 Specific COX I inhibitors: These drugs inhibit only COX I but not inhibit COX II, such as low-dose aspirin.

1.1.2 Nonspecific COX inhibitors: These drugs inhibit both COX I and COX II in little different concentrations. Log-dose response curve is similar including high-dose aspirin, indomethacin, piroxicam, diclofenac and ibuprofen,etc.

1.1.3 Preferential or selective COX II inhibitors: In dosages for inflammation and pain relief, drugs selectively inhibit COX II but inhibit COX I not significantly. If increasing dose, drug can also inhibit COX I such as meloxicam, nimesulide, nabumetone, etodolac and carprofen, etc.

1.1.4 Specific COX II inhibitors or COX II agents: Although increasing dose, drug can not inhibit COX I, such as celecoxib, rofecoxib, valdecoxib, parecoxib and etoricoxib, etc.

1.2 Indication and Dosage regimen of specific COX II inhibitors and approval date in US and Thailand.

The indications/dosage regimens/approval date in US and Thailand of specific COX II inhibitors were described as shown in Table 2.1-2.2.

Table 2.1: Summary of the indications/dosage regimens/approval date in US and Thailand of Celecoxib 100, 200 mg capsule (10)

Indication	Dosage Regimen	Approval Date in US	Approval Date in Thailand
Osteoarthitis (OA)	100 mg BID or 200 mg OD	31 Dec 1998	29 June 2000
Rheumatoid arthritis(RA)	100-200 mg twice daily	31 Dec 1998	29 June 2000
Reduces the number of adenomatous colorectal polyps in familial adenomatous polyposis patients as adjunct to usual care	400 mg twice daily	31 Dec 1998	29 June 2000
Primary Dysmenorrhea	400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed	18 Oct 2001	2002
Acute Pain - Surgical Dental Pain - Post operative surgical pain	400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed	18 Oct 2001	2002

Table 2.2: Summary of the indications/dosage regimens/approval date in US and Thailand of Rofecoxib 12.5, 25 mg, 50 mg, tablet, 12.5 mg/5ml and 25 mg/5 ml oral suspension. (10)

Indication	Dosage Regimen	Approval Date in US		Approval Date in Thailand		
		12.5, 25 mg tablet 12.5mg/5ml, 25 mg/5ml oral suspension	50 mg tablet	12.5, 25 mg tablet	12.5 mg/5 ml , 25 mg/5 ml	50 mg tablet
Osteoarthitis (OA)	12.5 mg OD, Max. doses 25 mg OD	20 May 1999	11 April 2002	14 December 2000	15 November 1999	26 November 2001
Rheumatoid arthritis(RA)	25 mg OD	11 April 2002	11 April 2002	28 January 2003	28 January 2003	28 January 2003
Primary Dysmenorrhea	Initial 50 mg OD Maintenance 25-50 mg OD Max. 50 mg OD treat at least 5 days	20 May 1999	11 April 2002	14 December 2000	15 November 1999	26 November 2001
Acute Pain - Surgical Dental Pain - Post operative surgical pain	Initial 50 mg OD Maintenance 25-50 mg OD Max. 50 mg OD treat at least 5 days	20 May 1999	11 April 2002	14 December 2000	15 November 1999	26 November 2001

Note : In Thailand Rofecoxib 12.5 mg/5ml , 25 mg /5ml oral suspension and 50 mg tablet is NC approved drug ,there are SMP for ADR monitoring.

Efficacy of Specific COX II inhibitors

The results based on our review indicated that in osteoarthritis, celecoxib was compared with naproxen (11), diclofenac (12), and rofecoxib(13-14). The results showed that they were more efficacious than placebo. Rofecoxib was compared with ibuprofen (16, 17), diclofenac (15,16), nabumetone (5) and naproxen (5). The results showed that they were more efficacious than placebo. One study reported that diclofenac efficacious was higher than rofecoxib 12.5 mg (16). Efficacy of celecoxib compared with rofecoxib and NSAIDs, and rofecoxib compared with NSAIDs in treatment of osteoarthritis was summarized as shown in Table 2.3.

In rheumatoid arthritis, celecoxib compared with naproxen (18) and diclofenac SR (19) were similar in anti-inflammatory activity. Rofecoxib compared with naproxen (20), the result found that they were similar in efficacious. Efficacy of celecoxib compared with rofecoxib and NSAIDs, and rofecoxib compared with NSAIDs in treatment of rheumatoid arthritis was described as given in Table 2.4.

In acute pain, celecoxib compared with rofecoxib (5) and ibuprofen (21), the result found that they were significantly greater than placebo. However, celecoxib more efficacious less than rofecoxib at 8-16 hours but celecoxib and rofecoxib were similar efficacy at 20 hours in Lumbar Laminectomy Pain (5). Rofecoxib compared with ibuprofen (22) and naproxen (23), the result found that they were significantly greater than placebo. Efficacy of celecoxib compared with rofecoxib and rofecoxib compared with NSAIDs in treatment of acute pain and dysmenorrhea was presented as shown in Table 2.5.

Data based on dysmenorrhea efficacy of celecoxib were not available. Rofecoxib compared with naproxen, the result showed that they were more efficacious than placebo during the first 8 hours (24). Efficacy of celecoxib compared with rofecoxib, and rofecoxib compared with NSAIDs in treatment of acute pain and dysmenorrhea was presented as shown in Table 2.5.

Another indication including Familial Adenomatous Polyposis (FAP), celecoxib could reduced the mean number of rectal and colon polyps in patients with FAP (25-26). Currently there are no clinical trials that have evaluated COX II inhibitors for the treatment or prevention of Alzheimer's Disease (AD)(27). Celecoxib should be clearly studied for skin cancer prevention indication (28). Alzheimer's Disease and skin cancer prevention indication were not approved for specific COX II inhibitor by US FDA. The results of summary of comparison clinical trial of efficacy for celecoxib and rofecoxib were presented as shown in Table 2.6.

Table 2.3: Summary of Clinical Efficacy Studies For Celecoxib and Rofecoxib in Osteoarthritis.

Study	Treatment			Pts	Wks	Results & Comments
	Celecoxib vs NSAID	Celecoxib vs Rofecoxib	Rofecoxib vs NSAID			
Bensen et al.,1999 (11)	Celecoxib 50 mg bid Celecoxib 100mg bid Celecoxib 200mg bid Naproxen 500mg bid Placebo	-	-	203 197 202 198 203	12	Celecoxib and naproxen more efficacious than placebo. Celecoxib 100mg and 200mg more efficacious than celecoxib 50mg
McKenna et al.,2001 (12)	Celecoxib 100mg bid Diclofenac 50 mg tid Placebo	-	-	201 199 200	6	Celecoxib and diclofenac more efficacious than placebo.
McKenna et al.,2001 (13)	-	Celecoxib 200mg od Rofecoxib 25mg od Placebo	-	63 59 60	6	Celecoxib and rofecoxib more efficacious than placebo.
Geba et al.,2002 (14)	-	Rofecoxib 25 mg od Rofecoxib 12.5mg od Celecoxib 200mg od Acetaminophen1g qid	-	95 96 97 94	6	Rofecoxib 25mg more efficacious than rofecoxib 12.5mg,celecoxib 200mg, acetaminophen 4 g
Cannon et al.,2000 (15)	-	-	Rofecoxib 12.5 mg od Rofecoxib 25 mg od Diclofenac 50 mg tid	259 257 268	1 years	Both rofecoxib doses and diclofenac were comparable efficacy.

Table 2.3: (cont.)

Study	Treatment			Pts	Weeks	Results & Comments
	Celecoxib vs NSAID	Celecoxib vs Rofecoxib	Rofecoxib vs NSAID			
Sagg et al., 2000 (16)	-	-	Rofecoxib 12.5mg od Rofecoxib 25 mg od Ibuprofen 800 mg tid Placebo	219 227 221 69	6	Both rofecoxib doses and ibuprofen were significantly greater than placebo.
Sagg et al., 2000 (16)	-	-	Rofecoxib 12.5 mg od Rofecoxib 25 mg od Diclofenac 50 mg tid	231 232 230	1 years	Rofecoxib 25 mg and diclofenac showed similar efficacy but rofecoxib 12.5 mg less efficacy than diclofenac.
Day et al.,2000 (17)	-	-	Rofecoxib 12.5 mg od Rofecoxib 25 mg od Ibuprofen 800mg tid Placebo	244 242 249 74	6	Both rofecoxib doses and ibuprofen were significantly greater than placebo.
Matherson et al., 2001 (5)	-	-	Rofecoxib 12.5 mg od Rofecoxib 25 mg od Nabumetone1500 mg/day Placebo	N= 341	6	Both rofecoxib doses and nabumetone were significantly greater than placebo.
Matherson et al., 2001 (5)	-	-	Rofecoxib 12.5 mg od Naproxen 500 mg bid	NA	NA	Rofecoxib and naproxen showed no differences in efficacious.

Table 2.4: Summary of Clinical Efficacy Studies For Celecoxib and Rofecoxib in Rheumatoid Arthritis.

Study	Treatment			Pts	Wks	Results & Comments
	Celecoxib vs NSAID	Celecoxib vs Rofecoxib	Rofecoxib vs NSAID			
Simon et al., 1999 (18)	Celecoxib 100mg bid Celecoxib 200mg bid Celecoxib 400mg bid Naproxen 500mg bid Placebo	-	-	240 235 218 225 231	12	Only celecoxib 200mg and 400 mg and naproxen were significantly better than placebo.
Emery et al.,1999 (19)	Celecoxib 200mg bid Diclofenac SR 75 mg bid	-	-	326 329	6	Similar anti-inflammatory and analgesic activity in both groups.
Bombardier et al.,2000 (20)	-	-	Rofecoxib 25 mg od Naproxen 500 mg bid	4047 4029	1 years	Rofecoxib and naproxen wer comparable efficacy.

Table 2.5: Summary of Clinical Efficacy Studies For Celecoxib and Rofecoxib in Acute Pain and Dysmenorrhea.

Study	Treatment			Pts	Wks	Results & Comments
	Celecoxib vs NSAID	Celecoxib vs Rofecoxib	Rofecoxib vs NSAID			
Malmstrom et al.,1999 (21)	-	Celecoxib200mg Rofecoxib50mg Ibuprofen400mg Placebo	-	91 90 46 45	Single dose	Efficacy for rofecoxib, celecoxib and ibuprofen greater than placebo. Onset of pain relief with rofecoxib and ibuprofen greater than celecoxib. Effect duration longer with rofecoxib in Dental Surgery Pain.
Matherson et al., 2001 (5)	-	Celecoxib200mg Rofecoxib50mg Placebo	-	N= 60	Single dose	Rofecoxib more efficacious higher than celecoxib at 8,12and 16hr. Both groups efficacious no significantly differences after 20hr in Lumbar Laminectomy Pain.
Morrison et al., 1999 (22)	-	-	Rofecoxib 50mg Ibuprofen 400 mg Placebo	50 51 50	Single dose	Initial efficacy for rofecoxib and ibuprofen similar; both better than placebo. Effect duration longer with rofecoxib in Post Surgical Dental Pain.
Reicin et al., 2001 (23)	-	-	Day1 Rofecoxib 50mg Day2-5 Rofecoxib 25mg Day2-5 Rofecoxib 50mg Naproxen 550 mg Placebo	 56 54 55 53	5 days	Rofecoxib 50 mg and naproxen were significantly better than placebo. Rofecoxib 25 mg was rated as between rofecoxib 50mg and placebo in Post Surgical Pain.
Morrison et al., 1999 (24)	-	-	Rofecoxib 25 mg initial followed by 25 mg daily as needed Rofecoxib 50 mg initial followed by 25 mg daily as needed Naproxen 550 mg initial follow q12hr Placebo	118 115 122 118	3 days	During the first 8 hours, both rofecoxib doses and naproxen more efficacious than placebo.

Table 2.6: Summary of Comparison Clinical Efficacy Studies For Celecoxib and Rofecoxib in Different Indications.

Type	Celecoxib vs NSAIDs	Rofecoxib vs NSAID	Celecoxib vs Rofecoxib
OA	Celecoxib and naproxen and diclofenac more efficacious than placebo.	Rofecoxib 25 mg and diclofenac showed similar efficacy but rofecoxib 12.5 mg less efficacy than Diclofenac. Rofecoxib and naproxen, nabumetone, ibuprofen more efficacious than placebo.	Rofecoxib 25mg more efficcious than rofecoxib 12.5mg and celecoxib 200mg. Celecoxib 200mg/day and rofecoxib 25 mg/day were efficacy significantly greater than placebo.
RA	Celecoxib (200mg/day, 400 mg/day) and naproxen and diclofenac SR more efficacious than placebo.	Rofecoxib and Naproxen were comparable efficacy.	-
Dysmenorrhea	-	Rofecoxib and naproxen more efficacious than placebo.	-
Acute Pain	-	Rofecoxib 50 mg and naproxen and ibuprofen were significantly better than placebo.	Efficacy for rofecoxib, celecoxib and ibuprofen greater than placebo.
FAP	Celecoxib 400mg efficacious greater than celecoxib 100mg and placebo.	-	-
AD	The investigators should be clearly study for this indication.	The investigators should be clearly study for this indication.	The investigators should be clearly study for this indication.
Skin Cancer	The investigators should be clearly study for this indication.	The investigators should be clearly study for this indication.	The investigators should be clearly study for this indication.

Adverse Effect of Specific COX II inhibitors

The result from our literature review showed that in upper gastrointestinal effect, celecoxib had incidence of gastroduodenal ulcer less than naproxen in rheumatoid arthritis (29). Celecoxib had incidence of gastroduodenal ulcer less than naproxen in osteoarthritis (11). Celecoxib had the rate of withdrawal for gastrointestinal-related adverse events less than diclofenac SR in rheumatoid arthritis (30). There was no significant difference in ulcer complications alone or combined with symptomatic ulcers between the celecoxib and NSAIDs (diclofenac and ibuprofen) when patients on low dose Aspirin ($\leq$ 325 mg/day) (31). The results of gastrointestinal adverse effects of celecoxib versus NSAIDs were presented in Table 2.7. Cumulative incidence over 12 months of rofecoxib was significantly lower than NSAIDs (Ibuprofen, Diclofenac, Nabumetone) in osteoarthritis (32,33). Rofecoxib had incidence of gastrointestinal events lower than naproxen in rheumatoid arthritis (20). The result of gastrointestinal adverse effects of rofecoxib vs NSAIDs was presented in Table 2.8.

The rate of myocardial infarction was not significantly different between rofecoxib and naproxen in patient not taking low-dose aspirin as secondary prophylaxis in rheumatoid arthritis (20). The incidence of thromboembolic cardiovascular events (myocardial infarction, stroke) was lower with rofecoxib than with diclofenac (15). The annualized rate for acute myocardial infarction was slightly higher in patients receiving rofecoxib compared with receiving celecoxib (34). The World Health Organization/ Uppsala Monitoring Center (WHO/UMC) reported information component (IC) of cardiovascular events of rofecoxib significantly higher than celecoxib (35).

In renal toxicity, celecoxib and rofecoxib are not recommended for use in patients with advanced renal disease. Patients at greatest risk for renal injury are renal impairment, heart failure, liver dysfunction, taking diuretics and/or ACE inhibitors, and the elderly. Kidney function should be monitored closely after initiating treatment with these agents, especially in high-risk populations (36).

In general adverse events, both celecoxib and naproxen had headache and upper respiratory tract infection (URTI) was the first and second common adverse events

(11). Rofecoxib and diclofenac in osteoarthritis, they had URTI, sinusitis, nausea, diarrhea and heartburn. The differences in incidence of GI adverse events were not statistically significant (15).

Table 2.7: Summaries Gastrointestinal Adverse Effects of Celecoxib Versus NSAIDs

Study	Type	Drugs	Pts	Weeks	Results
Bensen et al., 1999 (11)	OA	Celecoxib		12	Incidence of GI events
		50 mg bid	203		28%
		100 mg bid	197		27%
		200 mg bid	202		24%
		Naproxen 500 mg bid	198		32%
		Placebo	203		22%
Simon et al.,1999 (29)	RA	Celecoxib		12	Incidence of ulceration over 12 weeks
		100 mg bid	148		6%
		200 mg bid	145		4%
		400 mg bid	130		6%
		Naproxen 500 mg bid	137		26%
		Placebo	99		4%
Emery et al.,1999 (30)	RA	Celecoxib200 mg bid	326	24	Gastroduodenal ulcer was detected endoscopically 15% of Diclofenac SR and 4% of celecoxib group. (P<0.001) Abdominal pain was significantly lower in celecoxib (11%) than in diclofenac SR group (21%). (P<0.05)
		Diclofenac SR bid	329		
Silverstein et al.,2000 (31)	OA or RA	Celecoxib 400mg bid	3,987	2 Years	All patients, annualized incidence rates of ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.76% vs 1.45% (P=0.09) and 2.08% vs 3.45% NSAIDs (P=0.02)
		Ibuprofen 800 mg tid	1,985		
		Diclofenac 50mg tid	1,996		
					In patients not receiving aspirin, annualized incidence rates of ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.44% vs 1.27% (P=0.04) and 1.40% vs 2.90% (P=0.02).

Table 2.8: Summaries of Gastrointestinal Adverse Effects of Rofecoxib versus NSAIDs

Study	Type	Drugs	Pts	Weeks	Results
Langman et al.,1999 (32)	OA	Rofecoxib12.5 mg/d Rofecoxib 25 mg/d Rofecoxib 50 mg/d Ibuprofen 800mg tid Diclofenac50 mg tid Nabumetone1500mg/d Placebo	1,209 1,603 545 847 590 127 514	2 Years	Cumulative incidence rate of PUBs (GI Perforation, Gastroduodenal Ulcers, and GI Bleeding) over 12 months for rofecoxib vs NSAIDs were 1.33 vs 2.60 per 100 pt-years; RR 0.51 (95%CI, 0.26-1.00).
Watson et al.,2000 (33)	OA	Rofecoxib12.5 mg/d Rofecoxib 25 mg/d Rofecoxib 50 mg/d Ibuprofen 800mg tid Diclofenac50 mg tid Nabumetone1500mg/d Placebo	1,209 1,603 545 847 590 127 514	2 Years	Cumulative incidence rate of discontinuation due to GI AEs during 12 months for rofecoxib vs NSAIDs were 8.20 vs 12.03 per 100 pt-years; RR 0.70 (95%CI, 0.52-0.94)
Bombardier et al.,2000 (20)	RA	Rofecoxib 50mg/d Naproxen 500mg tid	4,047 4,029	1 Years	Incidence rate of confirmed upper GI events for rofecoxib vs NSAIDs were 2.1 vs 4.5 per 100 pt-years ; RR 0.5 (95%CI,0.3-0.6) Incidence rate of complicated confirmed upper GI events (Perforation, Obstruction and GI bleeding) for rofecoxib vs NSAIDs were 54.51 vs 63.56 per 100 pt-years; RR 0.88 (95%CI, 0.78-1.01).

Pharmacoeconomic Evaluation of Specific COX II Inhibitors

This part comprised cost of arthritis, pharmacoeconomic evaluation of celecoxib and rofecoxib, respectively. The last part is data on pharmacoecnomic evaluation of specific COX II inhibitors in Thailand.

1.1 Cost of Arthritis

In the US, Zabinski and Osterhaus (1999) illustrated that the average annual cost of arthritis-related care for rheumatoid arthritis was $2,162 per patient during July 1,1993 to June 30,1994. Average cost to osteoarthritis therapy was $543 per patient per year (37).

In UK, Hunsche, Jeremy and Bruce (2001) studied the burden of osteoarthritis and rheumatoid arthritis in Europe. Costs of arthritis in UK based on NHS perspective were estimated to be 495 million pounds sterling (1998: $US 1,316 million) in 1989. However, the Office of Health Economics estimated that the cost of arthritis would increase to 564 million pound sterling by 2001 in 1989 prices (38).

1.2 Pharmacoeconomic Evaluation of Celecoxib

In 2000, the Arthritis Cost Consequence Evaluation System (ACCES), a pharmacoeconomic model that were developed to predict and evaluate the costs and consequences associated with the use of celecoxib in patients with arthritis, compared with other NSAIDs and NSAIDs plus gastroprotective agents was studied by Pettitt and colleagues (39). This ACCES pharmacoeconomic model can be expected to reduce cost of concomitant for treatment of osteoarthritis and rheumatoid arthritis in Norway (40) and it can be expected to reduce the incidence of gastrointestinal adverse events, resource utilization and treatment costs in Sweden (41). In 2001, Burke and colleagues provided ACCES model to evaluate the economic impact in treatment of arthritis. This study found that celecoxib was expected to significantly reduce the economic costs of GI toxicity and its associated morbidity (42).

In Canada, Zabinski and colleagues (2001) used ACCES model to compare the costs and clinical consequences of treating patients with celecoxib or various NSAIDs/gastrointestinal (GI) co-therapy regimens for the management of osteoarthritis

and rheumatoid arthritis. The analysis based on a provincial Ministry of Health and considers patients aged ≥65 years. The result showed that NSAID-alone regimen was lowest cost ($262 Canadian dollars per patient per 6 months), followed by the celecoxib regimen ($Can 273), diclofenac/misoprostol ($Can 365), NSAID+$H_2$ receptor antagonist ($Can 413), NSAID+misoprostol ($Can 421), and NSAID+proton pump inhibitor ($Can 731), respectively. In additional, celecoxib was associated with the fewest GI-related deaths, hospitalized events, symptomatic ulcers, anemia, and upper GI distress (43).

In Switzerland, Jeremy and colleagues (2001) predicted cost effectiveness of celecoxib by applying model to compare the treatment cost and cost per adverse events of 6 months' treatment with the celecoxib, NSAID alone, NSAID+proton pump inhibitor (PPI), NSAID+H_2 receptor antagonist, NSAID+misoprostol and diclofenac/misoprostol. This study was healthcare payer perspective. They found that the lowest cost was celecoxib 435 Swiss francs (SwF), followed by NSAID alone SwF510, diclofenac/ misoprostol SwF 522, and other protected NSAID regimens between SwF 1,034 and SwF 1,415. Celecoxib was the lowest treatment cost of overall categories of GI risk among alternative treatment. The maximum cost per adverse event of NSAID alone was SwF440 (44).

In 2001, National Institute for Clinical Excellence (NICE) proposed that specific COX II inhibitors were not recommended for routine use in patients with rheumatoid arthritis or osteoarthritis. They should be used, in preference to standard NSAIDs, when clearly indicated as part of the management of rheumatoid arthritis or osteoarthritis only in patients who may be high risk of developing serious gastrointestinal adverse effects. NICE also indicated that the cost-effectiveness of the specific COX II inhibitors would be more favorable in high risk group (2).

In 2002, there was a study concerning with cost-effectiveness of celecoxib and rofecoxib in patients with osteoarthritis or rheumatoid arthritis by Maetzel and colleagues (45). They determined the cost-effectiveness of celecoxib 100-200 mg BID compared with diclofenac 50 mg TID and ibuprofen 800 mg TID, and rofecoxib 25 mg OD compared with naproxen 500 mg BID in patients with rheumatoid arthritis or osteoarthritis who are not on low-dose aspirin for the prevention of cardiovascular disease. The researchers used the Markov technique and extrapolated clinical trial results over a 5-year timeframe. Major events were 1) clinical upper gastrointestinal events, 2) complicated upper gastrointestinal events (excluding symptomatic ulcers), and 3) nonfatal

myocardial infarctions (MIs). Incremental cost-effectiveness, defined as the additional cost of the COX II inhibitors divided by its additional clinical benefit, was calculated from the perspective of the Ontario Ministry of Health in 1999 dollars. The results of this study found that:

(i) rofecoxib and celecoxib were not cost-effective treatments in patients at average risk of upper gastrointestinal events (symptomatic ulcers as shown by endoscopy or complicated UGI events—GI perforation, obstruction or major bleeding) or in a population with a mix of average risk and high risk patients;

(ii) rofecoxib and celecoxib were cost-effective treatments for patients who were considered at high risk for gastrointestinal events by having a history of upper gastrointestinal events;

(iii) rofecoxib and celecoxib became cost-effective treatments for patients without additional risk factors over the age of 76 for rofecoxib and 81 for celecoxib.

1.3 Pharmacoeconomics Evaluation of Rofecoxib

There are few formal data on the pharmacoeconomics of rofecoxib. One study reported that, in the treatment of patients with osteoarthritis aged ≥65 years, rofecoxib has a slightly higher acquisition cost than other commonly used NSAIDs ($1.60 vs $1.67 per patient per day, 2000 Canadian dollars): this leads to an incremental annual cost of $24.45 per patient using rofecoxib. These characteristics may double when rofecoxib is used to treat acute pain because higher dosages are used. However, rofecoxib is associated with a reduction of 0.0109 PUBs per patient per year, resulting in costs per PUB averted of $Can2247. These rates were sensitive to changes based on prophylactic GI comedication rates and drug costs, and were robust over a range of model assumptions (no data provided) (5).

Peterson and Cryer (1999) reported that patients with rheumatoid arthritis with a low risk (≈0.4%) of developing NSAID-induced GI complications, > 500 patients would need to be treated with rofecoxib to prevent 1 ulcer complication (assuming rofecoxib reduces the risk by 50%). Furthermore, based on 1999 US data, the yearly incremental cost of rofecoxib 25 mg/day compared with a generic NSAID such as naproxen is $US763 per patient, which approximate $US 400,000 per 500 patients. However, higher risk patients, such as those aged ≥ 75 years with a prior history of ulcer

and GI bleeding, have an approximate 5% risk of developing a complicated GI ulcer while taking an NSAID. Under the same assumptions, 40 patients would need to be treated with rofecoxib in order to prevent one ulcer complication, at a yearly incremental cost of $US 30,000 (46)

1.4 Pharmacoecnomic Evaluation of Specific COX II inhibitors in Thailand

In Thailand, no pharmacoeconomic evaluation of COX I I inhibitors was performed. Only cost analysis was conducted and reported in the following.

The first data were collected during 5 weeks period at orthopedics outpatient clinic. The selected prescriptions were only paid NSAIDs prescription. Prescriptions of the reimbursement group and non-reimbursement group were 1,042 (61.88%) and 642 (38.12%), respectively. There were marked differences between reimbursement group and non-reimbursement group in amount, type, group of NSAIDs and dispensing value aspects. The ratio of Essential Drug (ED) to Non-Essential Drug (NED) used in reimbursement group and non-reimbursement group was 1:6 and 1:2.6, respectively. In the reimbursement group, 53% of the expenditure of NSAIDs came from using selective COX II inhibitors. In the non-reimbursement group, however, 60% of the expenditure of NSAIDs came from using classical NSAIDs. All prescribing patterns could be classified as 8 patterns (289 styles). The most frequent prescribing pattern was single used of NSAID (67.03% of all prescription). Average dispensing value per prescription for reimbursement group was 532.89 baht but non-reimbursement group was 230.05 baht. Drug expenditure of selective and specific COX II inhibitors was 53.50%. There was a tendency to prescribe new generation NSAIDs more than the classical NSAIDs (6).

Another study focused on the problem of using c elecoxib and rofecoxib therapy in orthopedic outpatients of Lerdsin Hospital (7). The purpose of this study was to analyzed problem of using celecoxib and rofecoxib in terms of effectiveness, safety, economic impact and compliance of patients. The subjects of this study were 150 orthopedic outpatients. Average age was 55±1.0 years. Data based on the interviewing questionnaire were collected. They collected data during August 1, 2001 to November 30,

2001. The result showed that 32 % of patients had two co-morbidities, 48.7% of patients had no symptom or GI related effect and 81.3% of patient had ever taken prior NSAIDs. Sixty-five percentages were Civil Servant Medical Benefit Scheme (CSMBS) and 30% of treatment cost per visit was 601-900 Baht.

High Risk of Gastrointestinal Complications

The studies concerning high risk patient with gastrointestinal toxicity were reported in the following:

In 1999, Wolf and colleagues (47) reviewed the risk factors for the development of NSAID-associated gastroduodenal ulcers such as

1) Advanced age (linear increase in risk);

2) History of ulcer;

3) Concomitant use of corticosteroids;

4) Higher doses of NSAIDs, including the use of more than one NSAID;

5) Concomitant administration of anticoagulants;

6) Serious systemic disorder.

These factors were established risk factors. Possible risk factors were concomitant infection with *Helicobacter pylori*, cigarette smoking and consumption of alcohol.

In 2001, Laine (48) proposed risk factors for using NSAIDs. The risk factors vary widely in relationship to clinical features such as:

1) History of ulcers or gastrointestinal events may be the most important risk factor.

2) Increasing age, most studies document that the risk of NSAID associated GI complications increases with age.

3) Concomitant anticoagulant or steroid use, concurrent use of oral anticoagulants was reported to increase the risk of hospitalization for bleeding ulcer in NSAID user.

4) High dose NSAID use, a number of studies have clearly documented that the risk of upper GI complications increases with increasing doses of NSAIDs.

5) Severity of rheumatoid arthritis disability also may be associated with some increase in risk of NSAID-associated GI events.

6) Heart disease and other comorbidities also may increase the risk of NSAID-associated GI events, although supportive data are limited.

7) Duration of NSAID exposure, conflicting results have been reported on the relationship of the risk of GI events to the duration of exposure to NSAIDs. A number of epidemiologic studies have suggested that the risk of GI complications is highest in the first month of NSAID use. However, prospective experimental studies suggest a steady increase in the rate of GI complications over time.

8) Dyspepsia, upper GI symptoms are not good predictors of the development of upper GI events. Dyspepsia is extremely common in NSAID users. However, dyspepsia is extremely common on patients not taking NSAIDs.

The last risk factor was *Helicobacter pylori*, controversy exists regarding the interaction of *H.Pylori* infection and NSAID use. Most prospective endoscopic trials indicate that *H.Pylori* did not increase the risk of developing GI tract injury (including ulcers) in patients taking NSAIDs.

In July 2001, National Institute for Clinical Excellence (NICE) demonstrated factors associated with a high risk of development of gastrointestinal complications following NSAID therapy as

1) Age of 65 years and over;

2) Previous clinical history of gastroduodenal ulcers, gastrointestinal bleeding or gastroduodenal perforation;

3) Concomitant use of medications e.g. steroids and anti-coagulants;

4) Presence of serious co-morbidity such as cardio-vascular disease, renal or hepatic impairment, diabetes and hypertension;

5) Requirement for the prolonged use of maximum recommended doses of standard NSAIDs.

NICE also proposed that specific COX II inhibitors would be cost effective in patients at high risk of adverse gastrointestinal events.

They, therefore, proposed that only patients in the high risk categories above should be candidates for treatment with specific COX II inhibitors (2).