

National PBM Drug Monograph
Valdecoxib (Bextra®)
VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel

Introduction

Valdecoxib (Bextra®) is the third of the cyclooxygenase 2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs) to be approved by the FDA. Valdecoxib, like celecoxib and rofecoxib, primarily inhibits COX-2, and avoids inhibition of COX-1 at therapeutic concentrations¹⁻³. COX-1 is produced constitutively in most tissues and is responsible for prostaglandin synthesis important for the maintenance of the gastric mucosal barrier and platelet aggregation. COX-2 is an inducible isoform present at sites of inflammation⁴⁻⁸. COX-2 is also present in the kidneys, brain, and reproductive organs and may have some physiologic role in these tissues⁹⁻¹⁰. Endoscopic evidence does exist to support a safer gastrointestinal safety profile of the COX-2 inhibitors over certain nonselective NSAIDs (e.g. ibuprofen, naproxen, diclofenac). However, the correlation of endoscopic lesions/ulcers and incidence of clinically serious upper gastrointestinal events is unknown. Despite the available evidence, the FDA has chosen not to distinguish this group of agents from the NSAID class and has included the standard NSAID gastrointestinal warning in their product labeling. However, the FDA did approve the addition of data from the Vioxx Gastrointestinal Outcomes Research Trial (VIGOR) in which rofecoxib was associated with a lower risk of gastrointestinal complications and symptomatic ulcers compared to naproxen in rheumatoid arthritis sufferers not receiving low dose aspirin. The FDA also included data from that trial in which patients on rofecoxib had a significantly higher incidence of acute myocardial infarction versus those patients on naproxen.

Pharmacology/Pharmacokinetics⁽³⁾

Valdecoxib possesses anti-inflammatory, analgesic and antipyretic properties thought to occur as a result of inhibition of prostaglandin synthesis primarily by selective inhibition of COX-2. Valdecoxib can be taken without regard to meals since food does not effect valdecoxib's peak plasma concentration or bioavailability. However, time to peak plasma concentration was delayed 1-2 hours. Approximately 98% of valdecoxib is protein bound. Valdecoxib is metabolized in the liver via cytochrome P450 (CYP 450) 3A4 and 2C9 isoenzymes. It also undergoes glucuronidation within the liver. As a result of its extensive metabolism via CYP 450, concomitant use with known inhibitors of 3A4 and 2C9 can lead to decreased clearance and increased plasma concentrations of valdecoxib (e.g. itraconazole, erythromycin, fluconazole, ketoconazole, etc). Only about 5% of valdecoxib is excreted unchanged in the urine and feces. The elimination half-life of valdecoxib is 8-11 hours.

FDA Approved Indications and Off-label Uses⁽³⁾

Valdecoxib is FDA approved for the relief of the signs and symptoms of osteoarthritis (OA) and adults with rheumatoid arthritis (RA). It is also approved for the treatment of primary dysmenorrhea.

The company is also seeking approval for acute pain.

Current National Formulary Status⁽¹¹⁾

Celecoxib and rofecoxib are available on a non-formulary basis for patients meeting the approved VA criteria for use. Valdecoxib is not on the VA National formulary but will be incorporated into the COX-2 criteria for non-formulary use.

Dosage and Administration⁽³⁾

The recommended dose of valdecoxib for the relief of the signs and symptoms of osteoarthritis or rheumatoid arthritis is 10 mg once daily. Published and unpublished data demonstrate equal efficacy of the 10 mg and 20 mg dose. Therefore, there is no benefit to increasing the dose of valdecoxib above 10 mg daily for osteoarthritis or rheumatoid arthritis. The dose for primary dysmenorrhea is 20 mg twice daily, as needed. Valdecoxib may be taken without regard to meals.

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Special populations:

- No dosage adjustment is necessary in the elderly.
- No significant changes in valdecoxib clearance are seen regardless of severity of renal disease. However as with nonselective NSAIDs, use of valdecoxib may be associated with worsening renal impairment and is not recommended in patients with advance renal disease.
- Valdecoxib plasma concentrations are significantly increased in patients with moderate (Child-Pugh Class B) liver disease. Fluid retention was observed in clinical trials using higher than the usual recommended dose of valdecoxib. As a result, caution should be used when administering valdecoxib to patients with mild to moderate liver impairment and fluid retention. Valdecoxib is not recommended in patients with severe hepatic disease.

Adverse Effects⁽³⁾

Adverse effects, seen in clinical trials with valdecoxib, are similar to those seen with other NSAIDs. Table 1 represents data extracted from 7 studies in patients with OA or RA who received valdecoxib 10 or 20 mg daily, placebo or a positive control for 3 months or longer. Adverse effects listed in Table 1 occurred in ≥ 2% of patients.

Table 1

Adverse Event (Number treated)	Placebo (973)	Valdecoxib		<u>Total Daily Dose</u>		
		10 mg (1214)	20 mg (1358)	Diclofenac 150 mg (711)	Ibuprofen 2400 mg (207)	Naproxen 1000 mg (766)
Hypertension	0.6	1.6	2.1	2.5	2.4	1.7
Peripheral edema	0.7	2.4	3	3.2	2.9	2.1
Dizziness	2.1	2.6	2.7	4.2	3.4	2.7
Headache	2.1	4.8	8.5	6.6	4.3	5.5
Abdominal fullness	2	2.1	1.9	3	2.9	2.5
Abdominal pain	6.3	7	8.2	17	8.2	10.1
Diarrhea	4.2	5.4	6	10.8	3.9	4.7
Dyspepsia	6.3	7.9	8.7	13.4	15	12.9
Flatulence	4.1	2.9	3.5	3.1	7.7	5.4
Nausea	5.9	7	6.3	8.4	7.7	8.7

Table adapted from Bextra® product information

Precautions/Contraindications⁽³⁾

Precautions

- As with all NSAIDs, valdecoxib has been associated with borderline elevations in AST or ALT. Rare cases of severe liver toxicity have also been reported with NSAIDs. In a patient taking valdecoxib who develops elevated liver function tests and signs and symptoms of liver disease, providers should monitor for worsening liver function. In a patient who has clinical signs of liver toxicity or if systemic manifestations arise, valdecoxib should be discontinued.
- In those patients dependent upon renal prostaglandins for the maintenance of renal blood flow (e.g. impaired renal function, congestive heart failure, liver dysfunction, the elderly, and those taking diuretics or angiotensin converting enzyme inhibitors), administration of any NSAID may precipitate acute renal failure. As with other NSAIDs, caution should be used when prescribing valdecoxib in these individuals.
- Valdecoxib should be used with caution in patients with congestive heart failure or hypertension since fluid retention and edema can occur.

Warnings

- Serious gastrointestinal toxicity (e.g. bleeding, ulceration, and perforation) can occur at any time with or without warning in patients treated with NSAIDs. Approximately 2-4 % of patients taking NSAIDs on a regular basis for 1 year may develop GI ulcers, gross bleeding or perforation. NSAIDs should be used with extreme caution in those patients with a history of peptic ulcer disease and/or GI bleeding since their risk for a significant GI event is increased 10-fold. Other factors placing an individual at an increased risk for GI bleeding include use of warfarin or corticosteroids, duration of NSAID therapy, being elderly and poor general state of health.

Contraindications

- Valdecoxib is contraindicated in patients with a known hypersensitivity to valdecoxib.
- Valdecoxib should not be given to patients who have experienced asthma or allergic-type reactions after taking aspirin or NSAIDs since severe anaphylactoid reactions are possible in these patients.
- From postmarketing surveillance, Pharmacia has received reports of hypersensitivity reactions (e.g. anaphylactic reactions and angioedema) and serious skin reactions (e.g. Stevens-Johnsons syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and erythema multiforme) in individuals taking valdecoxib. These events have been reported in patients with and without a history of allergic-type reactions to sulfonamides. As a result of these reports, Pharmacia is currently in negotiations with the FDA regarding changes to the package insert. However, Pharmacia is currently recommending that valdecoxib not be given to patients who have experienced prior allergic-type reactions to sulfonamides. In addition, valdecoxib should be discontinued at the first sign of a skin rash or any other sign of hypersensitivity reaction.

Drug Interactions⁽³⁾

Valdecoxib is metabolized in the liver by CYP 450 isoenzymes (3A4 and 2C9) as well as via non-CYP 450 dependent pathways. It is not an important inhibitor of CYP 1A2, 3A4, or 2D6, but is a weak inhibitor of CYP 2C9 and 2C19. When valdecoxib was administered in combination with known inhibitors of CYP 3A4 and 2C9 (fluconazole, ketoconazole), valdecoxib’s area under the curve was increased. Since valdecoxib is a weak inhibitor of CYP 2C9, concomitant use with warfarin resulted in a significant increase in R-warfarin and S-warfarin. Although no guidance is provided in the prescribing information, caution as well as close monitoring is advised when combining valdecoxib with warfarin.

Efficacy Measures

Clinical Trials

To date, many of the clinical trials with valdecoxib are available only in abstract form.

Osteoarthritis abstracts: (OA) (Studies published in peer-reviewed journals are in bold type)

Citation	Fiechtner JJ, Sikes D, Recker D. A Double-blind, Placebo-Controlled Dose Ranging Study To Evaluate The Efficacy of Valdecoxib, A Novel COX-2 Specific Inhibitor, in Treating The Signs and Symptoms of Osteoarthritis of The Knee. Presented at the European Congress of Rheumatology (EULAR 2001): June 2001. ¹²
Funding Source	Pharmacia and Pfizer
Study Goals	To evaluate various doses of valdecoxib in treating the signs and symptoms of OA.
Methods	Design: Multicenter, double-blind, placebo-controlled, parallel group study in which 642 patients with OA were randomized to valdecoxib 0.5, 1.25, 2.5, 5 or 10 mg bid, valdecoxib 10 mg qd, naproxen 500 mg bid, or placebo bid for 6 weeks. Efficacy assessments: Patient’s assessment of pain and global assessment of arthritis (VAS), WOMAC OA index at baseline, 1, 2 and 6 weeks.
Results	All but the 0.5 mg bid dose of valdecoxib demonstrated greater efficacy in all measures studied vs. placebo (p≤0.05). Valdecoxib 5 mg bid, 10 mg bid and 10 mg qd were as effective as naproxen and better than placebo (p<0.004). No difference in ADRs, vitals or laboratory tests.

Conclusions	Valdecoxib 5 mg, 10 mg bid and 10 mg qd were the most effective doses and were equal to naproxen in managing the signs and symptoms of OA of the knee.
Comments	Abstract

ADRs-adverse drug reactions, VAS-visual analog scale, WOMAC-Western Ontario and McMasters Universities

Citation	Makarowski W, Zhao WW, Bevirt T, Recker DP. Efficacy and Safety of the COX-2 Specific Inhibitor Valdecoxib in the Management of Osteoarthritis of the Hip: A Randomized, Double-blind, Placebo-controlled Comparison with Naproxen. Osteoarthritis and Cartilage 2002;10:290-296¹³
Funding Source	Pharmacia and Pfizer
Study Goals	The efficacy and tolerability of valdecoxib was compared to naproxen in treating symptomatic OA of the hip.
Methods	Design: Multicenter, double-blind, placebo-controlled study in which 467 patients with OA of the hip were randomized to valdecoxib 5 mg qd, 10 mg qd, naproxen 500 mg bid or placebo for 12 weeks. Efficacy assessments: Patient and Physician’s global assessment of arthritis were measured at 2, 6 and 12 weeks.
Results	Both doses of valdecoxib produced significantly greater improvement in efficacy measures vs. placebo. Valdecoxib 10 mg qd was equally efficacious to naproxen during the study period and was numerically better than valdecoxib 5 mg qd. ADRs reported with valdecoxib were similar to those reported with placebo. Abdominal pain was reported more often in the naproxen vs. valdecoxib groups.
Conclusions	Valdecoxib 10 mg qd was equal to naproxen in treating symptomatic OA of the hip and better than valdecoxib 5 mg qd.
Comments	High rate of withdrawal from all groups (40% or >). Although not statistically significant, there were numerically higher numbers of withdrawals due to ADEs in the naproxen group vs. valdecoxib and higher numbers of withdrawal due to treatment failure in both valdecoxib groups vs. naproxen.

ADEs-adverse drug effects, ADRs-adverse drug reactions

Osteoarthritis abstracts focused on the GI safety profile of valdecoxib: (Studies published in peer-reviewed journals are in bold type)

Citation	Sikes DH Agrawal NM, Zhao WW, et al. Incidence of Gastroduodenal Ulcers Associated with Valdecoxib Compared with that of Ibuprofen and Diclofenac in Patients with Osteoarthritis. Eur J Gastroenterol Hepatol 2002;14:1101-1111.¹⁴																								
Funding Source	Pharmacia and Pfizer																								
Study Goals	Therapeutic doses of valdecoxib are COX-1 sparing as measured by incidence of endoscopic upper GI ulceration compared to ibuprofen and diclofenac.																								
Methods	Design: Mulicenter, double-blind, placebo-controlled, parallel group study in which 1052 patients with <10 erosions and no upper GI ulcers were randomized to valdecoxib 10 or 20 mg qd, ibuprofen 800 mg tid, diclofenac 75 mg SR bid or placebo for 12 weeks. Safety assessment: Pretreatment and final endoscopy at 12 weeks.																								
Results	Significantly less patients in the valdecoxib and placebo groups experienced gastroduodenal, gastric or duodenal ulcers vs. ibuprofen or diclofenac (p<0.05). Gastroduodenal ulcer rates were higher in patients >65 years and those receiving low dose aspirin in all treatment groups. ADEs (abdominal pain, constipation, diarrhea) were statistically greater with diclofenac compared to placebo. ADEs (constipation, dyspepsia) were statistically greater with ibuprofen than placebo. <table style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>Placebo (123)</th> <th>Valdecoxib 10 (142)</th> <th>Valdecoxib 20 (157)</th> <th>Ibuprofen (149)</th> <th>Diclofenac (145)</th> </tr> </thead> <tbody> <tr> <td>Gastroduodenal</td> <td>8 (4%)</td> <td>7 (4%)</td> <td>7 (4%)</td> <td>25 (14%)*</td> <td>25 (13%)*</td> </tr> <tr> <td>Gastric</td> <td>6 (3%)</td> <td>5 (3%)</td> <td>6 (3%)</td> <td>21 (11%)*</td> <td>20 (11%)*</td> </tr> <tr> <td>Duodenal</td> <td>3 (2%)</td> <td>2 (1%)</td> <td>1 (1%)</td> <td>6 (3%)</td> <td>7 (4%)</td> </tr> </tbody> </table> <p>*p<0.05 vs. placebo and valdecoxib 10 and 20 mg</p>		Placebo (123)	Valdecoxib 10 (142)	Valdecoxib 20 (157)	Ibuprofen (149)	Diclofenac (145)	Gastroduodenal	8 (4%)	7 (4%)	7 (4%)	25 (14%)*	25 (13%)*	Gastric	6 (3%)	5 (3%)	6 (3%)	21 (11%)*	20 (11%)*	Duodenal	3 (2%)	2 (1%)	1 (1%)	6 (3%)	7 (4%)
	Placebo (123)	Valdecoxib 10 (142)	Valdecoxib 20 (157)	Ibuprofen (149)	Diclofenac (145)																				
Gastroduodenal	8 (4%)	7 (4%)	7 (4%)	25 (14%)*	25 (13%)*																				
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Duodenal	3 (2%)	2 (1%)	1 (1%)	6 (3%)	7 (4%)																				
Conclusions	Valdecoxib is associated with a lower incidence of upper GI ulcers vs. nonselective NSAIDs (ibuprofen or diclofenac) in patients with OA.																								
Comments	Severity of ulcers or erosions (post-treatment) in each group was not provided. Unclear if endoscopic findings were similar at baseline between groups. No data was provided on whether patients were previously treated with NSAIDs. Not intent to treat analysis. Although the																								

	authors question the clinical relevance, the groups were not equal at baseline with regard to weight, H. Pylori positivity or duration of arthritis. The authors also noted that use of low dose aspirin ranged from 9-18% but did not break the percentages down for comparison between groups. The correlation of endoscopic lesions/ulcers and incidence of clinically serious upper gastrointestinal events is unknown.
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ADEs=adverse events

Citation	Kivitz A, Eisen G, Zhao WW, et al. Randomized, Placebo-controlled Trial Comparing Efficacy and Safety of Valdecoxib with Naproxen in Patients with Osteoarthritis. J Fam Pract 2002;51:530-537¹⁵												
Funding Source	Pharmacia and Pfizer												
Study Goals	The efficacy and upper GI safety of valdecoxib was compared to naproxen and placebo in patients with symptomatic OA of the knee.												
Methods	Design: Multicenter, double-blind, placebo-controlled trial in which 1019 patients with OA were randomized to valdecoxib 5 mg, 10 mg or 20 mg qd, naproxen 500 mg bid or placebo for 12 weeks. Efficacy assessments: Patient and Physician’s global arthritis assessment, Patient’s assessment of arthritis pain and the WOMAC were measured at baseline, 2, 6 and 12 weeks. Safety assessment: Pre and post treatment endoscopy.												
Results	Valdecoxib 10 and 20 mg qd produced significantly better improvements in efficacy measures vs. placebo (p<0.05) but similar to naproxen. Patients in the naproxen group experienced significantly more gastroduodenal ulcers than patients in valdecoxib 5 and 10 mg (p<0.05) but not valdecoxib 20 mg. <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>Placebo (205)</th> <th>Valdecoxib 5 (201)</th> <th>Valdecoxib 10 (206)</th> <th>Valdecoxib 20 (202)</th> <th>Naproxen (205)</th> </tr> </thead> <tbody> <tr> <td>Gastroduodenal ulcers</td> <td>8 (4%)</td> <td>6 (3%)*</td> <td>5 (3%)*</td> <td>10 (5%)</td> <td>18 (10%)</td> </tr> </tbody> </table> *p<0.05 vs naproxen		Placebo (205)	Valdecoxib 5 (201)	Valdecoxib 10 (206)	Valdecoxib 20 (202)	Naproxen (205)	Gastroduodenal ulcers	8 (4%)	6 (3%)*	5 (3%)*	10 (5%)	18 (10%)
	Placebo (205)	Valdecoxib 5 (201)	Valdecoxib 10 (206)	Valdecoxib 20 (202)	Naproxen (205)								
Gastroduodenal ulcers	8 (4%)	6 (3%)*	5 (3%)*	10 (5%)	18 (10%)								
Conclusions	Valdecoxib 10 mg and 20 mg qd, but not 5 mg, are as effective as naproxen in treating symptomatic OA of the knee. Valdecoxib 5 and 10 mg qd, but not 20 mg, demonstrated a lower number of endoscopically determined gastroduodenal ulcers compared to naproxen.												
Comments	Severity of ulcers for each group not provided. No data was provided on whether patients were previously treated with NSAIDs. No mention of factors that may increase risk for ulceration (age, concomitant drugs, history of peptic ulcer disease, etc). The correlation of endoscopic lesions/ulcers and incidence of clinically serious upper gastrointestinal events is unknown.												

WOMAC-Western Ontario and McMaster’s Universities

Rheumatoid Arthritis (RA) abstracts:

Citation	Bensen W, Weaver A, Espinoza L, et al. Efficacy and Safety of Valdecoxib in Treating the Signs and Symptoms of Rheumatoid Arthritis: A Randomized, Controlled Comparison with Placebo and Naproxen. Rheumatology 2002;41:1008-1016.
Funding Source	Pharmacia and Pfizer
Study Goals	To evaluate the efficacy and tolerability of 3 different doses of valdecoxib compared to naproxen and placebo in patients with RA.
Methods	Design: Multicenter, double-blind, placebo-controlled trial in which 1090 patients with RA were randomized to valdecoxib 10 mg, 20 mg or 40 mg qd, naproxen 500 mg bid or placebo for 12 weeks. Efficacy assessments: American College of Rheumatology-Responding Index (ACR-20) at 2, 6 and 12 weeks. The number of ACR responders were analyzed using the Cochran-Mantel-Haenzel test.
Results	The ACR-20 at all follow up periods was significantly improved for all 2 doses of valdecoxib vs. placebo (p<0.01) and similar to naproxen. Authors note that patients reported more dyspepsia with naproxen vs. valdecoxib 10 and 20 mg qd. However the overall rate of ADEs were not different between active groups but greater than placebo.
Conclusions	Valdecoxib 10 mg and 20 mg qd was similar in efficacy to naproxen in treating the signs and symptoms of RA.
Comments	For the ACR-20 responders, there was no difference between any of the 3 valdecoxib doses. However, valdecoxib 10 and 20 mg daily were better tolerated than the 40 mg dose.

ADEs-adverse drug events

Rheumatoid Arthritis (RA) abstracts focusing on the GI safety profile of valdecoxib:

Citation	Goldstein JL, Kent JD, Zhao WW, et al. Reduced Incidence of Gastroduodenal Ulcers with Valdecoxib Compared to Diclofenac in Patients with Rheumatoid Arthritis: A Multicenter Trial. Presented at the American College of Gastroenterology 66 th Annual Scientific Meeting: October 2001. ¹⁷																
Funding Source	Pharmacia and Pfizer																
Study Goals	To compare the incidence of gastroduodenal ulcers with valdecoxib vs. diclofenac in patients with RA.																
Methods	Design: Multicenter, double-blind, parallel group trial in which 636 patients with RA were randomized to valdecoxib 20 mg qd, 40 mg qd or diclofenac 75 mg bid for 26 weeks. Safety assessment: Post treatment endoscopy																
Results	Significantly more patients in the diclofenac group developed gastroduodenal ulcers than in either of the valdecoxib groups*. <table border="1"> <thead> <tr> <th></th> <th>Valdecoxib 20 (213)</th> <th>Valdecoxib 40 (215)</th> <th>Diclofenac (208)</th> </tr> </thead> <tbody> <tr> <td>Gastroduodenal</td> <td>12 (6%)</td> <td>8 (4%)</td> <td>34 (16%)</td> </tr> <tr> <td>Gastric</td> <td>5 (2%)</td> <td>5 (2%)</td> <td>26 (13%)</td> </tr> <tr> <td>Duodenal</td> <td>9 (4%)</td> <td>3 (1%)</td> <td>12 (6%)</td> </tr> </tbody> </table> <p>*p<0.05</p>		Valdecoxib 20 (213)	Valdecoxib 40 (215)	Diclofenac (208)	Gastroduodenal	12 (6%)	8 (4%)	34 (16%)	Gastric	5 (2%)	5 (2%)	26 (13%)	Duodenal	9 (4%)	3 (1%)	12 (6%)
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Gastroduodenal	12 (6%)	8 (4%)	34 (16%)														
Gastric	5 (2%)	5 (2%)	26 (13%)														
Duodenal	9 (4%)	3 (1%)	12 (6%)														
Conclusions	The authors conclude that both doses of valdecoxib are associated with a lower risk for upper GI ulcers compared to diclofenac in patients with RA.																
Comments	Abstract. No pretreatment endoscopy was performed to determine presence of ulcers or erosions in RA patients. No data was provided on whether patients were previously treated with NSAIDs. No mention of factors that may increase risk for ulceration (age, concomitant drugs, history of peptic ulcer disease, etc). Severity of ulcers for each group not provided. The correlation of endoscopic lesions/ulcers and incidence of clinically serious upper gastrointestinal events is unknown.																

Osteoarthritis and Rheumatoid arthritis abstracts

Citation	Agrawal N, Paperiello A, Zhao WW, et al. Supratherapeutic Doses of Valdecoxib Have a Reduced Incidence of Gastroduodenal Ulcers Compared with Conventional Therapeutic Doses of Naproxen in Osteoarthritis and Rheumatoid Arthritis Patients. Gut; Vol. 49 (suppl III); November 2001; abstract no. 2157. ¹⁸																
Funding Source	Pharmacia and Pfizer																
Study Goals	Compare the incidence of gastroduodenal ulcers with valdecoxib 20 and 40 mg bid and naproxen 500 mg bid in patients with OA and RA.																
Methods	Design: Multicenter, double-blind, parallel group study in which 1217 patients with OA and RA were randomized to valdecoxib 20 mg bid, 40 mg bid or naproxen 500 mg bid for 14 weeks. Patients with <10 gastroduodenal erosions and no ulcers at pretreatment endoscopy were included in the final analysis (n=1064). Safety assessment: Pre and post treatment endoscopy.																
Results	<table border="1"> <thead> <tr> <th></th> <th>Valdecoxib 20 mg bid (345)</th> <th>Valdecoxib 40 mg bid (355)</th> <th>Naproxen 500 mg bid (364)</th> </tr> </thead> <tbody> <tr> <td>All patients</td> <td>15 (4%)</td> <td>27 (8%)</td> <td>66 (18%)*</td> </tr> <tr> <td>OA patients</td> <td>6 (3%)</td> <td>16 (9%)**</td> <td>36 (20%)*</td> </tr> <tr> <td>RA patients</td> <td>9 (5%)</td> <td>11 (6%)</td> <td>30 (16%)*</td> </tr> </tbody> </table> <p>*p<0.05 vs. valdecoxib 20 and 40 mg, **p<0.05 vs. valdecoxib 20 mg</p>		Valdecoxib 20 mg bid (345)	Valdecoxib 40 mg bid (355)	Naproxen 500 mg bid (364)	All patients	15 (4%)	27 (8%)	66 (18%)*	OA patients	6 (3%)	16 (9%)**	36 (20%)*	RA patients	9 (5%)	11 (6%)	30 (16%)*
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OA patients	6 (3%)	16 (9%)**	36 (20%)*														
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Conclusions	Long-term use of supratherapeutic doses of valdecoxib demonstrates a significantly lower risk of gastroduodenal ulcers in patients with OA and RA vs. naproxen.																
Comments	No data was provided on whether patients were previously treated with NSAIDs. No mention of factors that may increase risk for ulceration (age, concomitant drugs, history of peptic ulcer disease, etc.). Severity of ulcers for each group not provided. The correlation of endoscopic lesions/ulcers and incidence of clinically serious upper gastrointestinal events is unknown.																

Primary dysmenorrhea abstracts

Citation	Daniels S, Talwalker S, Torri S, Snabes M, et al. Valdecoxib, A Cyclooxygenase-2 Specific Inhibitor, is Effective in Treating Primary Dysmenorrhea. Obstet Gynecol 2002;100:350-358.¹⁹																									
Funding Source	Pharmacia and Pfizer																									
Study Goals	To determine if valdecoxib provides effective relief of menstrual pain due to primary dysmenorrhea compared to naproxen.																									
Methods	Design: Two single-center, double-blind, cross-over studies in 238 patients with moderate to severe menstrual pain were randomized to valdecoxib 20 mg or 40 mg, naproxen sodium 550 mg or placebo in a single dose phase, then bid/prn for up to 3 days. Patients who completed all four cycles were included in the pooled efficacy analysis (n=180). Efficacy assessments: Time weighted sums of pain relief (TOTPAR) and of Pain Intensity Differences (SPID) were assessed at 8 and 12 hours after the single dose.																									
Results	TOTPAR and SPID at 8 and 12 hrs (Least square means) <table border="1"> <thead> <tr> <th></th> <th>Placebo (180)</th> <th>Valdecoxib 20 mg (180)</th> <th>Valdecoxib 40 mg (180)</th> <th>Naproxen (180)</th> </tr> </thead> <tbody> <tr> <td>TOTPAR 8 hr</td> <td>14.58</td> <td>19.25*</td> <td>20.87*</td> <td>20.63*</td> </tr> <tr> <td>TOTPAR 12 hr</td> <td>22.94</td> <td>29.97*</td> <td>32.92*+</td> <td>32.10*</td> </tr> <tr> <td>SPID 8 hr</td> <td>6.89</td> <td>10.03 *</td> <td>10.63*</td> <td>10.69*</td> </tr> <tr> <td>SPID 12 hr</td> <td>11.07</td> <td>15.62*</td> <td>16.95*+</td> <td>16.67*</td> </tr> </tbody> </table> <p>*p≤0.05 vs. placebo, +p≤0.05 vs. valdecoxib 40 mg</p>		Placebo (180)	Valdecoxib 20 mg (180)	Valdecoxib 40 mg (180)	Naproxen (180)	TOTPAR 8 hr	14.58	19.25*	20.87*	20.63*	TOTPAR 12 hr	22.94	29.97*	32.92*+	32.10*	SPID 8 hr	6.89	10.03 *	10.63*	10.69*	SPID 12 hr	11.07	15.62*	16.95*+	16.67*
	Placebo (180)	Valdecoxib 20 mg (180)	Valdecoxib 40 mg (180)	Naproxen (180)																						
TOTPAR 8 hr	14.58	19.25*	20.87*	20.63*																						
TOTPAR 12 hr	22.94	29.97*	32.92*+	32.10*																						
SPID 8 hr	6.89	10.03 *	10.63*	10.69*																						
SPID 12 hr	11.07	15.62*	16.95*+	16.67*																						
Conclusions	Valdecoxib 20 and 40 mg were equal to naproxen and better than placebo in pain assessments measured. Valdecoxib 40 mg produced statistically greater pain relief than valdecoxib 20 mg at 12 hours.																									
Comments	No mention of reason for significant loss to follow up. No intention to treat analysis used. No mention of details on dosing for up to 3 days with any agents.																									

Acute pain abstracts : (Studies published in peer-reviewed journals are in bold type)

Citation	Daniels SE, Desjardins PJ, Talwalker S, et al. The Analgesic Efficacy of Valdecoxib vs. Oxycodone/Acetaminophen After Oral Surgery. JADA 2002;133:611-621.²³																														
Funding Source	Pharmacia and Pfizer																														
Study Goals	To compare the analgesic efficacy and safety of valdecoxib with oxycodone/acetaminophen in patients who have undergone oral surgery (2 or > impacted molars)																														
Methods	Design: Single dose, double-blind, double-dummy, placebo-controlled study in 406 patients undergoing extraction of 2 or > impacted third molars. Patients were randomized to receive one dose of valdecoxib 20 or 40 mg, oxycodone 10 mg/acetaminophen 1000 mg or placebo. There were 2 centers that performed the same study (Study A n=205 and Study B n=201). Efficacy Assessment: Time to meaningful analgesia and time to rescue medication over a 24 hour period. Safety Assessment: Number and frequency of ADEs reported.																														
Results	The results are provided for both studies. Onset of analgesia was significantly shorter in the active groups compared to placebo (median time to analgesia 28-34 minutes p<0.05) In Study A, oxycodone/acetaminophen provided a statistically significant shorter time to analgesia compared to either dose of valdecoxib. However, the difference was 3 minutes. There was no difference between active groups in Study B. <u>Rescue medication:</u> <table border="1"> <thead> <tr> <th></th> <th>Patients requiring Rescue Med(%)</th> <th>Median Time to Rescue Analgesia (hr:min)</th> </tr> </thead> <tbody> <tr> <td colspan="3">Study A</td> </tr> <tr> <td>Placebo (n=52)</td> <td>85</td> <td>1:05*</td> </tr> <tr> <td>Oxycodone/Ace (n=51)</td> <td>55</td> <td>11:17**</td> </tr> <tr> <td>Valdecoxib 20 mg (n=52)</td> <td>46</td> <td>>24 hr***</td> </tr> <tr> <td>Valdecoxib 40 mg (n=50)</td> <td>24</td> <td>>24 hr</td> </tr> <tr> <td colspan="3">Study B</td> </tr> <tr> <td>Placebo (n=51)</td> <td>90</td> <td>1:04*</td> </tr> <tr> <td>Oxycodone/Ace n=51)</td> <td>78</td> <td>6:04**</td> </tr> <tr> <td>Valdecoxib 20 mg (n=49)</td> <td>57</td> <td>10:58</td> </tr> </tbody> </table>		Patients requiring Rescue Med(%)	Median Time to Rescue Analgesia (hr:min)	Study A			Placebo (n=52)	85	1:05*	Oxycodone/Ace (n=51)	55	11:17**	Valdecoxib 20 mg (n=52)	46	>24 hr***	Valdecoxib 40 mg (n=50)	24	>24 hr	Study B			Placebo (n=51)	90	1:04*	Oxycodone/Ace n=51)	78	6:04**	Valdecoxib 20 mg (n=49)	57	10:58
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	Valdecoxib 40 mg (n=50) 44 >24 *P<0.05 vs all active treatments, **p<0.05 vs. valdecoxib 40 mg (study A) or valdecoxib 20 or 40 mg (Study B), ***p<0.05 vs. valdecoxib 40 mg.
Conclusions	Both valdecoxib 20 and 40 mg provided pain relief comparable to oxycodone/acetaminophen but with a longer duration of analgesic action. Patients in either valdecoxib group experienced a significantly lower incidence of opioid related ADEs (nausea, vomiting, dizziness) vs. oxycodone/acetaminophen.
Comments	In Study B, more patients in the placebo group had complete bony impaction of their molars vs. the active treatment groups. Intent to treat statistics were used.

ADE=adverse drug effects

Citation	Fricke J, Varkalis J, Zwillich S, et al. Valdecoxib is More Efficacious Than Rofecoxib in Relieving Pain Associated with Oral Surgery. Am J Ther 2002;9:89-97.²⁴
Funding Source	Pharmacia and Pfizer
Study Goals	To compare the analgesic efficacy and safety of valdecoxib with rofecoxib in patients who have undergone oral surgery (removal of 2 or > third molars with at least bony impaction).
Methods	Design: Double-blind, placebo-controlled, randomized, parallel group study conducted over a period of 24 hours in patients who had undergone removal of 2 or more third molars. One of these extractions had to require some bone removal. A total of 203 patients were randomized to receive a single dose of valdecoxib 40 mg, rofecoxib 50 mg or placebo. Efficacy Assessments: Onset of analgesia, pain intensity levels, time-weighted sum of total pain, sum of pain intensity difference, % of patients requiring rescue medications, and patient's global evaluation. Safety Assessments: Monitoring treatment emergent ADEs.
Results	There were no statistically significant differences between active groups with regard to onset of analgesia. Pain intensity was reported to be lowered statistically more in the valdecoxib vs. rofecoxib group. Authors reported a lower number of patients required rescue medication in the valdecoxib vs. rofecoxib group (see comments below). There were no differences with regard to ADEs with the exception of a higher "dry sockets" reported in the rofecoxib vs. placebo groups (p<0.05).
Conclusions	Authors concluded that patients in the valdecoxib group experienced lower pain intensity and greater satisfaction after a single dose than those on rofecoxib. They also stated that valdecoxib demonstrated superior efficacy with regard to number of patients requiring rescue analgesia (see comments below). Both active treatments were well tolerated.
Comments	Patients in the valdecoxib group could request a second dose of valdecoxib 40 mg. However, patients on rofecoxib 50 mg could request a second dose but received placebo (the same number of people requested a second dose of medication in each active treatment arm). As a result, the evaluation of difference in rescue medication between groups is flawed. Furthermore, patients assessment of study medication is also flawed.

ADEs=Adverse drug effects

Citation	Daniels DE, Talwalker S, Hubbard C, et al. Pre-Operative Valdecoxib, a COX-2 Specific Inhibitor, Provides Effective and Long Lasting Pain Relief Following Oral Surgery. Presented at the American Society of Anesthesiologists Annual Meeting; October 2001. ²⁰	
Funding Source	Pharmacia and Pfizer	
Study Goals	To evaluate the analgesic efficacy, duration of action and safety of a single pre-operative dose of valdecoxib in patients undergoing extraction of 2 ipsilateral impacted third molars.	
Methods	Design: Double-blind, placebo-controlled study in 284 patients who were having oral surgery to remove 2 ipsilateral impacted third molars. Patients received valdecoxib 10, 20, 40, 80 mg or placebo 60-75 minutes before the procedure. Efficacy assessment: Time to rescue medication and patient's global evaluation of study medication. Percentage of patients requiring rescue medications and global evaluation were analyzed using the Fisher's exact test. Safety assessment: Not mentioned	
Results	Median Time to Rescue Med Med (hr:min)	Patients Requiring Rescue Med (%)
	Placebo (n=56)	2:59 95
	Valdecoxib 10 mg (n=54)	9:04* 67*
	Valdecoxib 20 mg (n=56)	13:06* 57*
	Valdecoxib 40 mg (n=56)	>24:00*± 32*
	Valdecoxib 80 mg (n=56)	>24:00*± 41*

	*p<0.001 vs. placebo, +p<0.01 vs. valdecoxib 10 mg, ±p,0.01 vs. valdecoxib 20 mg
Conclusions	Preoperative valdecoxib was effective for pain following oral surgery. The 40 mg dose of valdecoxib was significantly better than placebo and valdecoxib 10 and 20 mg. Increasing the dose to 80 mg did not provide any additional benefit.
Comments	The authors mentioned that ADRs with valdecoxib was lower than those reported in the placebo groups and no-dose dependent increase in ADRs were seen (single-dose study).

ADRs=adverse drug reactions

Citation	Dejardins PJ, Talwalker S, Hubbard RC, et al. Pre-Operative Administration of Valdecoxib, a Potent COX-2 Specific Inhibitor, Provides Effective Post-Operative Analgesia. Presented at the American Society of Anesthesiologists Annual Meeting, October 2001. ²¹															
Funding Source	Pharmacia and Pfizer															
Study Goals	To evaluate the analgesic efficacy, duration of action and safety of a single pre-operative dose of valdecoxib in patients undergoing bunionectomy.															
Methods	Design: Double-blind, placebo-controlled study in 223 patients undergoing bunionectomy were given a pre-operative dose of 20, 40, or 80 mg of valdecoxib or placebo 45 to 75 minutes prior to surgery. The procedure lasted approximately 35-45 minutes. Efficacy assessment: Time to rescue medication and patient’s global evaluation of study medication. The percentage of patients requiring rescue medications was followed over 24 hours and analyzed with the Fisher’s exact test. The global assessment was analyzed by Cochrane-Mantel-Haenszel test. Safety assessment: Not mentioned.															
Results	<table border="1"> <thead> <tr> <th></th> <th>Median Time to Rescue Med Med (hr:min)</th> <th>Patients Requiring Rescue Med (%)</th> </tr> </thead> <tbody> <tr> <td>Placebo (n=54)</td> <td>3:24</td> <td>100</td> </tr> <tr> <td>Valdecoxib 20 mg (n=56)</td> <td>7:04**</td> <td>88*</td> </tr> <tr> <td>Valdecoxib 40 mg (n=55)</td> <td>8:03**</td> <td>78**</td> </tr> <tr> <td>Valdecoxib 80 mg (n=55)</td> <td>8:05**</td> <td>71**</td> </tr> </tbody> </table> <p>*p<0.01 vs. placebo, **p<0.001 vs. placebo</p>		Median Time to Rescue Med Med (hr:min)	Patients Requiring Rescue Med (%)	Placebo (n=54)	3:24	100	Valdecoxib 20 mg (n=56)	7:04**	88*	Valdecoxib 40 mg (n=55)	8:03**	78**	Valdecoxib 80 mg (n=55)	8:05**	71**
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Conclusions	Time to rescue medication was longer with the valdecoxib 40 and 80 mg doses compared to valdecoxib 20 mg and placebo. Although no statistical significance was provided for the 2 higher doses of valdecoxib vs the 20 mg dose. Increasing the dose of valdecoxib from 40 to 80 mg did not translate into greater efficacy.															
Comments	The authors mentioned that ADRs with valdecoxib were lower than those reported in the placebo groups and no-dose dependent increase in ADRs were seen (single-dose study).															

ADRs=adverse drug reactions

Citation	Camu F, Beecher T, Talkwalker, et al. Valdecoxib, A COX-2 Specific Inhibitor, is an Efficacious, Opioid-Sparing Analgesic in Patients Undergoing Hip Arthroplasty. <i>Am J Ther</i> 2002;9:43-51. ²²																				
Funding Source	Pharmacia and Pfizer																				
Study Goals	To study the opioid sparing properties, the analgesic efficacy and safety of valdecoxib vs. placebo in patients undergoing primary hip arthroplasty.																				
Methods	Design: Multi-center, double-blind, multiple-dose, placebo-controlled study in which 217 patients undergoing primary hip arthroplasty were given valdecoxib 20 or 40 mg bid or placebo starting 1-3 hours prior to surgery. All patients received morphine via patient-controlled analgesia (PCA) within 120 minutes after surgery was completed. Patients requiring further analgesia beyond that prescribed in the study protocol were withdrawn. Efficacy assessments: Total amount of morphine used via PCA, patient’s global evaluation and the percentage of patients requiring morphine at scheduled time points over the 48 hour period following the first dose of study medication. The total amount of morphine used was analyzed by analysis of covariance. The percentage of patients requiring PCA and patient’s global evaluation was analyzed by the Cochran-Mantel-Haenszel test. Safety assessment: Reported ADRs, routine laboratory analyses and physician examination.																				
Results	<table border="1"> <thead> <tr> <th></th> <th colspan="2">Total morphine (mg ± SD) consumed by bolus and PCA 24 hrs after surgery Mean ± SD</th> <th>Morphine 48 hrs after surgery</th> </tr> <tr> <th></th> <th colspan="2">(% less than placebo)</th> <th>Mean + SD (% less than Placebo)</th> </tr> </thead> <tbody> <tr> <td>Placebo</td> <td>31.6 ± 15.13</td> <td></td> <td>49.4 ± 3.4</td> </tr> <tr> <td>Valdecoxib 20 bid</td> <td>20.7 ± 13.59 (-34.5%)*</td> <td></td> <td>28.1 ± 2.4 *</td> </tr> <tr> <td>Valdecoxib 40 bid</td> <td>19.4 ± 13.32 (-38.6%)*</td> <td></td> <td>29.3 ± 2.5 *</td> </tr> </tbody> </table>		Total morphine (mg ± SD) consumed by bolus and PCA 24 hrs after surgery Mean ± SD		Morphine 48 hrs after surgery		(% less than placebo)		Mean + SD (% less than Placebo)	Placebo	31.6 ± 15.13		49.4 ± 3.4	Valdecoxib 20 bid	20.7 ± 13.59 (-34.5%)*		28.1 ± 2.4 *	Valdecoxib 40 bid	19.4 ± 13.32 (-38.6%)*		29.3 ± 2.5 *
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	*Statistically significant vs. placebo (p<0.001)
Conclusions	Patients receiving valdecoxib required approximately 40% (20 mg) less morphine within the first 48 hours after surgery. A greater number of patients in the valdecoxib 20 and 40 mg groups (97% and 96%, respectively) rated their study medication as good or excellent compared to 77% of patients on placebo (p<0.001). There were no significant differences with regard to safety between groups. There were no differences between 20 mg and 40 mg valdecoxib.
Comments	Authors commented that those patients in the valdecoxib arms of the study tolerated the medication as well as those receiving morphine alone. Only 195 patients completed the study. Intent to treat statistics were not used.

ADRs=adverse drug reactions

Acquisition Cost (FSS pricing) (does not account for BPA pricing)

COX-2 Specific Agent	Cost per Day (\$)	Cost per Month (\$)
<u>Celecoxib</u>		
100 mg bid	1.74	52.20
200 mg qd	1.49	44.70
200 mg bid	2.98	89.40
<u>Meloxicam**</u>		
7.5 mg qd	0.79	23.70
15 mg qd	0.88	26.40
<u>Rofecoxib</u>		
12.5 mg qd	1.51	45.30
25 mg qd	1.52	45.60
50 mg qd*	2.22	--
<u>Valdecoxib</u>		
10 mg qd	1.74	52.20
20 mg qd	1.74	52.20
20 mg bid	3.48	104.40

*Dose not recommended for long-term use, **May inhibit COX-1 at high therapeutic doses (e.g. >15 mg daily)

Conclusions

Valdecoxib is the third cyclooxygenase-2 specific inhibitor to be approved by the FDA. From published data, valdecoxib appears to possess efficacy equal to the nonselective NSAIDs (naproxen, ibuprofen and diclofenac). The gastrointestinal safety of valdecoxib has been evaluated in two studies using endoscopy in which authors observed that valdecoxib 10 mg daily was associated with a statistically lower incidence of gastroduodenal ulcers compared to naproxen, ibuprofen or diclofenac. Valdecoxib is extensively metabolized via cytochrome P450 (3A4 and 2C9), and has the potential for drug-drug interactions, although the clinical significance of this is not known. Valdecoxib’s acquisition price (full tablet) is higher than the other available agents. However, the prices listed in the above table may be lower for all COX-2s depending upon the market share in a particular VISN (based upon BPA contracts). As with the other available COX-2 agents, it is recommended that valdecoxib not be added to the VA National Formulary or VISN formularies but be available on a nonformulary basis for those patients meeting criteria for using COX-2 inhibitors (similar to the process currently used for other available COX-2 inhibitors).

Prepared by Cathy Kelley, Pharm.D., BCPS

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