Drug Class Review

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Final Update 4 Evidence Tables

November 2010

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Update 3: November 2006
Update 2: May 2004
Update 1: September 2003
Original Report: May 2002
The literature on this topic is scanned periodically

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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Abbreviations used in evidence tables

Abbreviation	Meaning
ACR	American College of Rheumatology
ACT	Active-control trial
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ASA	Aspirin
AST	Aspartate aminotransferase
AUSCAN	Australian/Canadian Osteoarthritis Hand Index
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
bid	Twice daily
BMI	Body mass index
CCT	Controlled clinical trial
CI	Confidence interval
CLASS	Celecoxib Long-term Arthritis Safety Study
CNS	Central nervous system
COAD	Chronic obstructive airways disease
COX-2 inhibitors	Cyclooxygenase-2 inhibitors
CR	Controlled release
CV	Cardiovascular
CVS	Cardiovascular system
d	Day
DB	Double-blind
DHEP	Diclofenac hydro xyethyl pyrrolidine plasters
dL	Deciliter
DMSO	Dimethyl sulfoxide
EA	Extra articular
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection fraction
ER	Extended release
FDA	US Food and Drug Administration
FU	Follow-up
g	Gram

Abbreviation	Meaning
GI	Gastrointestinal
GI	Gastrointestinal
GP	General practitioner
h	Hour
HDL-C	High density lipoprotein cholesterol
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health related quality-of-life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
INR	international normalized ratio
IPA	Isolated inflammatory periarticular
IR	Immediate release
ITT	Intention-to-treat
L	Liter
LA	Long acting
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last Observation Carried Forward
LS means	Least squares means
MANCOVA	Multivariate analysis of covariance
mcg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
mo	Month
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NR	Not reported
NS	Not significant
NSD	No significant difference
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome measures in rheumatoid arthritis clinical trials
OR	Odds ratio
P	*P* value

Abbreviation	Meaning
P	Placebo
PA	Peri-articular
PCT	Placebo-controlled trial
PGA	Patient global assessment
PPY	Per person year
qd	Once daily
QOL	Quality of life
RA	rheumatoid arthritis
RCT	Randomized controlled trial
RR	Relative risk
SB	Single-blind
SD	Standard deviation
SE	Standard error
SR	Sustained release
tid	Three times daily
VAS	Visual analog scale
vs.	Compared with (versus)
WD	Withdrawal
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XR	Extended release
y	Year

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Altman 2009 U.S. (Fair)	Men and women ≥40 years with diagnosis of primary OA in their dominant hand. Following ACR criteria, OA was defined as nodal enlargement in ≥2 of 10 joints.	A: Diclofenac sodium gel 1% 2 g qd B: Placebo (Vehicle) For 8 weeks	Rescue medication (acetaminophen 500 mg tablets) at a maximum dose of 4 mg qd	64 years Male: 23% White: 89% Asian: 0.7% Black: 3.9% Other: 6.3%	Right handed: 91.2% Painful CMC-1 joint: 71.4% Painful DIP/PIP (Digits 2-3): 78.2% Currently treated with NSAIDs before screening visit: 51.7% Kellgren-Lawrence grade of 3: 52%	385

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Altman 2009 U.S. (Fair)	51/3/385	Diclofenac versus Placebo Change from baseline at Week 6 mean, (SD), (%), p value vs placebo: OA pain intensity: -33.7 (27.8), (-45.8%) vs -26.7 (28.0), (-36.3), p=0.023 Total AUSCAN score mean: -25.9 (25.1), (-38.5%) vs -18.6 (26.2), (-27.9%), p=0.006 Pain index: -26.1 (25.6), (-39.4%) vs -20.1 (26.5), (-30.1%), p=0.021 Stiffness index: -25.2 (28.7), (-38.2%) vs- 17.2 (30.0), (-25.8%), p=0.005 Functional index: -25.8 (26.1), (-38.0%) vs -17.8 (26.9), (26.7%), p=0.005 Global rating of disease: -23.1 (27.0), (40.1%) vs 16.3 (28.0), (-28.8%), p=0.023 Change from baseline at Week 8 mean, (SD), (%), p value vs placebo: OA pain intensity: -35.5 (28.9), (-48.2%) vs -29.6 (29.5), (-40.2%), p=0.06 Total AUSCAN score: -26.7 (26.6), (-39.7%) vs -20.5 (27.3), (30.7%), p=0.028 Pain index: -27.2 (26.9), (-41.0%) vs -22.5 (27.8), (-33.7%), p=0.09 Stiffness index: -26.6 (30.0), (-40.3%) vs -21.1 (30.5), (-31.7%), p=0.048 Global rating of disease: -24.2 (28.1), (-42.0%) vs -18.8 (29.2), (-33.3%), p=0.11

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Altman 2009 U.S. (Fair)	Diclofenac vs placebo At least one treatment-emergent AE: 52.0% vs 43.9% GI AE: 7.6% vs 3.7% Headache: 11.1% vs 10.2% Back pain: 6.1% vs 7.5% Arthralgia: 3.5% vs 7.0% Pain in extremity: 3.5% vs 3.2% Sinusitis: 3.0% vs 0.5% Neck pain: 3.0% vs 0.5% Application site paresthesia: 2.5% vs 1.1% Pharyngolaryngeal pain: 2.5% vs 0% Diarrhea: 2.0% vs 1.1% Cough: 2.0% vs 1.1% Upper respiratory tract infection: 2.0% vs 0.5%	Diclofenac vs Placebo Total: 25 (12.6%)vs 26 (13.9%) Due to AE: 10 (5%)vs 4 (2.1%)	Novartis Consumer Health Inc	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Baer 2005 Canada (Fair)	Men and women, age 40–85 years, with radiologically confirmed primary OA of at least one knee and a flare of pain at baseline following discontinuation of prior therapy (oral NSAID or acetaminophen used at least 3 days per week during the previous month). Excluded if they had secondary arthritis related to systemic inflammatory arthritis, recent corticosteroid use, ongoing use of prohibited medication (NSAID, other oral analgesic, muscle relaxant, or low-dose antidepressant for any chronic pain management, glucosamine or chondroitin)	A: Topical diclofenac solution (Pennsaid) B: Vehicle control solution (carrier with no diclofenac) 40 drops 4 times daily directly to the painful knee(s), without massage, for 6 weeks	ASA (≤ 325 mg/day) was permitted for cardiovascular prophylaxis; acetaminophen (up to four 325-mg tablets per day) was permitted for residual knee or other body pain throughout the treatment period, but not during the washout period prior to baseline assessment or during the week prior to final assessment at week 6.	64.8 years Male: 43.5% White: 82.9% Black: 5.1% Oriental: 2.3%	Weight: 86.7 kg Height: 1.65 m Heart rate: 74.2 bpm BP: 135.6/80.5 Total x-ray score: 7.3 Baseline pain score: 12.9 Baseline physical function score: 40.5 Baseline stiffness score: 5.2 PGA score: 3.2 Patients treating two knees at baseline: 62% Patients treating two knees at final: 80.1%	216

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Baer 2005 Canada (Fair)	60/0/212	Topical diclofenac vs vehicle-control Pain Mean change in score: -5.2 vs -3.3 (p=0.003) Mean difference in change: 1.9 (95% CI, 0.7 to 3.2) Physical function Mean change in score: -13.4 vs -6.9 (p=0.001) Mean difference in change: 6.5 (95% CI, 2.5 to 10.5) PGA Mean change in score:-1.3 vs -0.7 (p=0.0001) Mean difference in change: 0.6 (95% CI, 0.2 to 0.9) Stiffness Mean change in score: -1.8 vs -0.9 (p=0.002) Mean difference in change: 0.9 (95% CI, 0.3 to 1.4) Pain on walking Mean change in score: -1.2 vs -0.8 (p=0.014) Mean difference in change: 0.4 (95% CI, 0.1 to 0.7) 50% Reduction in pain: 43.8% vs 25.2% (p=0.004) Good or very good PGA response: 43.8% vs 16.8% (p<0.0001)

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Baer 2005 Canada (Fair)	Topical diclofenac vs vehicle-control <u>GI Reaction</u> Abdominal pain: 4 (3.7%) vs 1 (0.9%) Constipation: 1 (0.9%) vs 1 (0.9%) Diarrhea: 1 (0.9%) vs 0 (0%) Dyspepsia: 4 (3.7%) vs 1 (0.9%) Gastritis: 1 (0.9%) vs 0 (0%) Melena: 0 (0%) vs 1 (0.9%) Nausea: 1 (0.9%) vs 2 (1.8%) <u>Application-Site Skin Reaction</u> Dry skin/skin irritation: 42 (39%) vs 23 (21.1%); p=0.004 Rash: 2 (1.9%) vs 4 (3.7%) Paresthesia: 2 (1.9%) vs 2 (1.8%) Pruritus: 0 (0%) vs 2 (1.8%) <u>Other Reaction</u> Headache: 6 (5.6%) vs 10 (9.2%) Halitosis: 2 (1.9%) vs 0 (0%) Taste Perversion: 4 (3.7%) vs 2 (1.8%)	Topical diclofenac vs vehicle-control Total: 21 (19.6%) vs 39 (35.8%); p=0.008 Due to AE: 9 (8.4%) vs 9 (8.3%)	Dimethaid Health Care Ltd.	

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Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Barkhuizen, 2006 USA (Fair)	Male/Female 18-75 years old with AS with axial involvement and requiring NSAID during previous 30 days, with or without enthesopathy, large peripheral synovitis, psoriasis, pain intensity >50mm on a 100m VAS, no analgesic 8 hours or antiinflammatory 72 hours prior to study start, negative pregnancy test and continued use of effective contraception	A. Celecoxib 200 mg po qd B. Celecoxib 400 mg po qd C. Naproxen 500 mg bid D. Placebo	Acetaminophen up to 2000mg/day	40-45 years (mean 44.6 years) Male: 73.8% Caucasian: 76.6% Asian: 4.1% African American: 1.6% Other: 17.7%	Height: 170.7 cm Weight: 82.5 kg Patient's global assessment of pain intensity, mean: 71.9 Patient's global assessment of disease activity, mean: 66.6	611

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Barkhuizen, 2006 USA (Fair)	NR/203/408	Placebo vs Celecoxib 200mg vs Celecoxib 400 mg vs Naproxen LS mean changes from baseline to Week 12 in Pain Intensity Score (VAS): -9.9 vs -29.5 vs -30.0 vs -36.3 (p<0.001 for all active treatments vs placebo) LS mean changes from baseline to Week 12 in Disease Activity Score (VAS): -4.2 vs -21.1 vs -22.2 vs -27.6 (p<0.001 for all active treatments vs placebo; p<0.05 naproxen vs celecoxib 200 mg) LS mean changes from baseline to Week 12 in Functional Impairment (BASFI) Score (VAS): 3.1 vs -8.5 vs -12.1 vs -15.8 (p<0.001 for all active treatments vs placebo; p<0.01 naproxen vs celecoxib 200 mg) Physician's global assessment of disease activity, LS mean change from baseline to Week 12: -5.75 vs -18.7 (p ≤0.05 vs placebo) vs -23.4 (p≤0.05 vs placebo) vs -26.7 (p≤0.05 vs placebo and celecoxib 200 mg) Nocturnal Pain (VAS), LS mean change from baseline to Week 12: -3.05 vs -20.3 (p≤0.05 vs placebo) vs -22.3 (p≤0.05 vs placebo) vs -28.5 (p≤0.05) BASDAI, LS mean change from baseline to Week 12: -1.74 vs -15.4 (p≤0.05 vs placebo) vs -19.5 (p≤0.05 vs placebo) vs -22.9 (p≤0.05 vs placebo) Morning stiffness, min, median, change from baseline to Week 12: 0 vs -5 (p≤0.05 vs placebo) vs -20 (p≤0.05 vs placebo) vs -30 (p≤0.05 vs placebo and celecoxib 200 mg) CRP, mg/l, LS mean, change from baseline to Week 12: 1.17 vs -2.46 (p≤0.05 vs placebo) vs -2.64 (p≤0.05 vs placebo) vs -3.60 (p≤0.05 vs placebo)

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Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Barkhuizen, 2006 USA (Fair)	Placebo vs Celecoxib 200mg vs Celecoxib 400 vs Naproxen Any event: 82 (52.6%) vs 73 (53.3%) vs 85 (52.8%) vs 78 (49.7%) Headache: 11 (7.1%) vs 7 (5.1%) vs 13 (8.1%) vs 3 (1.9%) Nausea: 3 (1.9%) vs 4 (2.9%) vs 9 (5.6%) vs 7 (4.5%) Nasopharyngitis: 4 (2.6%) vs 10 (7.3%) vs 9 (5.6%) vs 5 (3.2%) Dermatitis: 3 (1.9%) vs 3 (2.2%) vs 8 (5.0%) vs 0 (0.0%) Arthralgia: 0 (0.0%) vs 5 (3.6%) vs 6 (3.7%) vs 1 (0.6%) Dyspepsia: 5 (3.2%) vs 6 (4.4%) vs 6 (3.7%) vs 11 (7.0%) Diarrhea: 3 (1.9%) vs 5 (3.6%) vs 5 (3.1%) vs 6 (3.8%) Fatigue: 5 (3.2%) vs 3 (2.2%) vs 3 (1.9%) vs 5 (3.2%) Upper respiratory tract infection: 7 (4.5%) vs 3 (2.2%)vs 3 (1.9%) vs 5 (3.2%) Sinusitis: 4 (2.6%) vs 0 (0.0%) vs 2 (1.2%) vs 5 (3.2%) Constipation: 2 (1.3%) vs 0 (0.0%) vs 1 (0.6%) vs 5 (3.2%) Sore throat: 5 (3.2%) vs 1 (0.7%) vs 0 (0.0%) vs 1 (0.6%)	203; 32 (11 placebo, 3 celecoxib 200 mg, 9 celecoxib 400 mg, 9 Naproxen)	Pfizer	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Barthel 2009 U.S. (Fair)	Ambulatory men and women ≥35 years with OA in one or both knees according to ACR criteria and with symptom onset ≥6 months before screening.	A:. Diclofenac sodium gel 1% 4 g qd B: Placebo For 12 weeks	Rescue medication (acetaminophen 500 mg tablets) at a maximum dose of 8 tablets (4 mg qd)	59.5 years Male: 22.3% Ethnicity: NR	BMI: 31.3 kg/m2	492

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Barthel 2009 U.S. (Fair)	45/5/491	Diclofenac vs Placebo Mean change in WOMAC pain from baseline at 12 weeks: -5.0 vs -4.0, p=0.01 Mean change in WOMAC function from baseline at 12 weeks: -15.0 vs -10.9, p=0.001 Change in global rating of disease from baseline at 12 weeks: -27.0 vs -18.2, p=0.001 Reduction in pain on movement from baseline at week 4: -27.7 vs -20.1 m.m; p<0.002 reflecting 44% reduction relative to baseline vs 32% reduction relative to placebo % OARSI response based on WOMAC pain index at week 12: 64.0% vs 51.7%, p=0.006 % OARSI response based on pain on movement at week 12: 64.8% vs 49.2%, p=0.003 Global evaluation of treatment at 12 weeks, mean (SD): 2.23 (1.43) vs 1.86 (1.43), p=0.007 Rescue drug use over entire study: 91.3% vs 92.4%, p=Weeks 0.600 Weeks with no rescue drugs, mean (SD): 4.33 (4.45) vs 3.46 (4.21), p=0.04

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Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Barthel 2009 U.S. (Fair)	Diclofenac vs Placebo Any AE: 60.2% vs 53.8% Severe AE: 5.1% vs 5.9% GI AE: 5.9% vs 5.0% AE occurring in ≥3% of randomized patients: Headache 13.8% vs 14.3% Arthralgia 13.4% vs 8.8% Back pain: 9.1% vs 6.7% Dermatitis: 4.3% vs 1.7% Skin Dryness : 0.4% vs 0.8% Eczema: 0.0% vs 0.4% Erythema: 0.4% vs 0.4% Papules: 0.4% vs 0.0% Pruritus: 1.6% vs 0.4% Unspecified reaction: 0.4% vs 0.0% Pain: 4.3% vs 2.9% Nasopharyngitis: 3.5% vs 5.9% Upper RTI: 3.5% vs 5.5% Sinusitis: 3.5% vs 2.5% Cough 0.4% vs 3.4%	Diclofenac vs placebo Total: 45 vs 60 Due to AE: 13 (5.1%)vs 9 (3.8%)	Novartis consumer health, Parsippany, NJ	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Bookman 2007 Canada (Fair)	Men and women 18-80 years with primary OA in at least 1 knee and at least moderate pain. Excluded patients with secondary arthritis related to syphilitic neuropathy, ochronosis, metabolic bone disease or acute trauma; for use of corticosteroids, oral analgesic or glucosamine, or another topical product at the application site.	A: Topical diclofenac solution (1.5% wt/wt diclofenac sodium in a carrier containing dimethyl sulfoxide) B: Vehicle-control solution (the carrier containing dimethyl sulfoxide but no diclofenac) C: Placebo solution (a modified carrier with a token amount of dimethyl sulfoxide for blinding purposes but no diclofenac) For 4 weeks	ASA (≤ 325 mg/d) was permitted for cardiovascular prophylaxis; use of acetaminophen (up to two 325 mg tablets qd) was permitted for other body pain or residual knee pain throughout the washout and study periods, except during the 24 hours immediately before the baseline and final WOMAC assessments.	61.8 years Male: 36.4% Ethnicity: NR	Weight: 83.3 kg Height: 1.66 m <u>Topical diclofenac vs vehicle-control vs placebo</u> Patients treating 2 knees: 38% vs 49% vs 51% (p=0.09) Radiographic analysis showed NSD between the treatment groups in the distribution of severity of joint-space narrowing and marginal osteophytes within each knee compartment	248

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Bookman 2007 Canada (Fair)	39/0/247	Topical diclofenac vs vehicle-control vs placebo WOMAC LK3.0 OA Index <u>Pain</u> Change from baseline, mean (95% CI): -3.9 (-4.8 to -2.9; p<0.05) vs -2.5 (-3.3 to -1.7; p=0.023) vs -2.5 (-3.3 to -1.7; p=0.016) Percent change from baseline: -42.9 vs -26.9 vs -26.6 <u>Physical function</u> Change from baseline, mean (95% CI): -11.6 (-14.7 to -8.4; p=0.002 compared with vehicle and p=0.014 compared with placebo) vs -5.7 (-8.3 to -3.2) vs -7.1 (-9.3 to -4.4) Percent change from baseline: -39.3 vs -18.7 vs -23.0 <u>Stiffness</u> Change from baseline, mean (95% CI): -1.5 (-1.9 to -1.1; p=0.015 compared with vehicle and p=0.002 compared with placebo) vs -0.7 (-1.2 to -0.3) vs -0.6 (-1.0 to -0.2) Percent change from baseline: -40.5 vs -20.0 vs -16.2 <u>Pain on walking</u> Change from baseline, mean (95% CI): -0.8 (-1.1 to -0.6; p=0.003 compared with vehicle and p<0.015 compared with placebo) vs -0.4 (-0.6 to -0.2) vs -0.6 (-0.8 to -0.4) Percent change from baseline: -44.4 vs -21.1 vs -30.0 <u>PGA:</u> Sum, mean (95% CI): 6.7 (6.1 to 7.4; p<0.05) vs 7.8 (6.9 to 8.6) vs 7.8 (7.2 to 8.5)

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bookman 2007 Canada (Fair)	Topical diclofenac vs vehicle-control vs placebo <u>At application site:</u> Dry skin: 36% (p=0.001 compared with vehicle-control group and p<0.0001 compared with placebo) vs 14% (p<0.01 compared with placebo) vs 1% Paresthesia: 14% vs 22% (p<0.01 compared with placebo) vs 6% Rash: 13% (p<0.05 compared with placebo) vs 8% vs 4% Pruritus: 11% vs 8% vs 4% <u>GI and other:</u> Constipation: 1% vs 1% vs 1% Diarrhea: 1% vs 2% vs 4% Dyspepsia: 7% vs 5% vs 6% Nausea: 0% vs 5% vs 1% Vomiting: 0% vs 1% vs 1% Halitosis: 5% vs 1% vs 0% Body odor: 2% vs 0% vs 0%	Topical diclofenac vs vehicle-control vs placebo Total: 10 (12%) vs 14 (17.5%) vs 15 (17.9%) Due to AE: 5 (6%) vs 3 (3.8%) vs 0 (0%; p=0.06)	NR (though competing interests were disclosed)	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Bruhlmann 2003 Switzerland	Men and women between 18-85 years affected by symptomatic OA of the knee.	A: 1.3% DHEP Patch (corresponding to 1% of diclofenac sodium salt) bid B: Placebo For 14 days	Paracetamol 500 mg tablets allowed as rescue	64.4 years Male: 41.7% Ethnicity: NR	Target knee (Left): 45.6% Target knee (Right): 54.4% Symptomatic involvement: Bilateral: 43.7% Unilateral left: 21.4% Unilateral right: 35%	103

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Bruhlmann 2003 Switzerland	10/2/103	DHEP patch vs placebo Lequesne index at baseline: 10.2 (3.3) vs 10.4 (3.5) Lequesne index at day 14: 6.9 (3.2) vs 9.0 (3.9), p<0.01 (between group as well as compared to baseline) Proportion of patients with reduction in Lequesne score at day 14: 32% vs 15% Spontaneous pain as measured on a numeric rating scale at baseline: 5.7 (1.5) vs 5.6 (1.5) Spontaneous pain as measured on a numeric rating scale at day 14: 2.1 (1.8) vs 3.9 (2.1), p< 0.01 between group as well as compared to baseline Walking time (sec) at baseline: 16.3 (6.7) vs 16.3 (4.2) Walking time (Sec) at day 14: 13.3 (4.3) vs 14.5 (3.4), p<0.01 from baseline, NS between groups Paracetamol consumption throughout the study: 22% vs 33% Patient judgment (p<0.05) Excellent: 24.5% vs 8.9% No efficacy: 10.2% vs 17.8% Physician Judgment (p<0.01) Excellent: 10.2% vs 8.9% No efficacy: 8.2% vs 20%

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Bruhlmann 2003 Switzerland	DHEP patch vs Placebo Patient judgment of Good or Excellent: 91.8% vs 93.4% Physician judgment of good or excellent: 95.9% vs 93.5% % reporting AE: 4 (7.8%) vs 3 (5.8%)	DHEP patch vs Placebo Total: 3 (5.9%) vs 7 (13.9%) Due to AE: 1 (2%) vs 2 (3.8%) Rush: 2 (3.9%) vs 1 (2%)	NR	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Chan, 2007 China	Patients with upper gastro-intestinal bleeding and taking non-selective NSAIDs for arthritis	200 mg bid celecoxib for all patients Group A: 20 mg esomeprazole bid Group B: Placebo For 12 mos	Antacids, paracetamol, Non-NSAID analgesics, and disease-modifying anti-rheumatic drugs	71 yrs % Male: 48.4% NR (could be 100% Asian)	Gastric ulcers: 57.5% Duodenal ulcer: 35% Gastric and duodenal More than 1 episode of ulcer bleeding: 18.7% Types of arthritis: OA: 86.4% RA: 2.2% Others: 11.4%	273

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Chan, 2007 China	45/1/237	Combined treatment (celecoxib +esomeprazole) vs control group (celecoxib+placebo) % of patients with decrease in hemoglobin of 20g/L: 0 vs 9 (6.6%) Global assessment of disease activity at baseline mean, (SD): 3.2 (0.7) vs 3.1 (0.8) Global assessment of disease activity at 12 mos: mean, (SD): 2.4 (0.8) vs 2.4 (0.7), change from baseline -0.8 vs -0.7, p<0.0001, p=0.85 between groups Patient's assessment on a VAS at baseline mean (SD): 63.9 (18.9) vs 60.0 (18.9) Patient's assessment on a VAS at 12 mos: 46.6 (19.0) vs 43.3 (17.7), change from baseline -17.3 vs 17.0, p<0.0001, p=0.74 between groups

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Chan, 2007 China	Combined treatment (celecoxib +esomeprazole) vs control group (celecoxib+placebo) % patients with recurrent ulcer bleeding: 0 vs 12 (8.9%) [95% CI, 4.1 to 13.7], p=0.0004 Cumulative incidence of lower gastro-intestinal bleeding: 3.0% (95% CI 0.1 to 5.8) vs 1.6% (95% CI -0.6 to 3.7) (p=0.46) Renal failure: 2.9% vs 2.9%, p=1.00 Unstable angina: 0.7% vs 0%, p=1.00 Stroke: 0% vs 1.5%, p=0.25 Heart failure: 0.7% vs 0.7%, p=1.00 Peripheral vascular disease: 0% vs 0.7% Others (pneumonia, COAD, hypoglycemia, hypocalcemia, hyponatremia, vertigo, head injury, knee arthritis, carcinoma of the larynx): 5.1% vs 5.1%, p=0.72 Deaths: 0.7% (pneumonia) vs 1.5% (head injury, core pulmonale), p=0.62 Hypertension: 18.2% vs 20.6%, p=0.63 Dyspepsia: 5.1% vs 9.6%, p=0.16 Peripheral edema: 3.6% vs 7.4%, p=0.18 Skin allergy: 0.7% vs 0.7%, p=1.00	Combined treatment (celecoxib +esomeprazole) vs control group (celecoxib+placebo) Total: 23 (17%) vs 22 (16%) Due to AE: 8 (5.8%) vs 10 (7.4%)	Grant from Research Grant Council of Hong-Kong (CUHK4455)	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Chan, 2010 (CONDOR) Multinational Good	Patients tested negative for helicobacter pylori, aged 60 years and older or 18 years or older with previous gastroduodenal ulceration	A. Celecoxib 200mg BID B. Diclofenac slow release 75 mg BID +Omeprazole for 6 mo	Antacids and non-NSAID analgesic drugs, including paracetamol upto 4 gms/day and histamine 2 receptor antagonists≤ 3 days per week. Prednisolone ≤10 mg daily, disease-modifying antirheumatic drugs or biologic treatments were only allowed if patients had been taking a stable dose for 12 or more weeks at randomization.	65 yrs Female: 82% White: 54.6% Black: 2.4% Asian: 13.6% Hispanic: 20.7% Other: 8.7%	Region of origin Western Europe: 20% South America: 39% Asia: 13% Easter Europe: 28% Haemoglobin (g/L): 140 Haematocrit:41% History of gastroduodenal ulcer or ulcer bleeding :19% Previous helicobacter pylori infection: 21.5% Comorbidity (includes coronary hear disease or heart failure, diabetes mellitus, hypertension, chronic lung diseases, chronic liver diseases, deep vein thrombosis, kidney diseases and history of anaemia	4484

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Chan, 2010 (CONDOR) Multinational Good	1133/NR/4484	Celecoxib vs diclofenac plus omeprazole % of patients reaching primary endpoint (composite of clinically significant events occuring throughout the GI tract 0.9% (95% CI, 0.5 to 1.3) vs 3.8 (95% CI 2.9 to 4.3), difference 2.9%, 2.0 to 3.8%, p<0.0001. Hazard ratio was 4.3 (2.6-7.0) in favor of celecoxib Clinically significant events through GI tract, total: 0.9% vs 3.6% Gastroduodenal haemorrhage: 0.1% vs 0.1% Gastric outlet obstruction: 0% vs 0% Gastroduodenal, small bowel or large bowel perforation:0% vs 0% Small bowel haemorrhage: 0% vs 0% Large bowel haemorrhage: 0% vs 0% Total clinically significant anaemia of defined GI origin: 0.2% vs 1.1% -Gastroduodenal ulcer or erosions: 0.2% vs 0.9% Clinically significant anaemia of presumed occult GI origin including possible small bowel blood loss: 0.4% vs 2.4% Haemoglobin decrease of 20g/L, n (%): 15 (0.7%) vs 77 (3.4%). Among them, haemoglobin concentration lower than 115 g/L: 10% vs 90% LSM change from baseline to visit 6 in patient's global assessmentof arthritis: improvement of 0.75 (0.02) vs 0.77 (0.02) Clinically significant events throughout GI tract plus symptomatic ulcers: 1% vs 5%, p<0.0001 % of patients with moderate to severe abdominal symptoms at month 6: 16% vs 19%, p=0.03

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Chan, 2010 (CONDOR) Multinational Good	Celecoxib vs diclofenac plus omeprazole Death: 2 (due to pulmonary embolism and bronchopneumonia) vs 2 (cardiac arrest) Patients with AE: 51% vs 58% Patients with treatment related AE: 25% vs 33% Patients with serious AE: 3% vs 3% Patients with serious treatment related AE: 1% vs <1% types of secondary AE Celecoxib group: 1stable angina, 2 transient ischaemic attacks, 1 peripheral arterial event, 4 venous thrombosis Diclofenac plus omeprazole: 1 transient ischaemic attack	Celecoxib vs diclofenac plus omeprazole Total withdrawals: 22.7% vs 27.8% Withdrawals due to AE: 10.4% vs 13.6% Withdrawals due to GI related AE: 6% vs 8%	Pfizer	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Dahlberg 2009 Scandinavia (Good)	Men and women ≥60 years with OA of the hip or knee with a functional capacity of I-III. Excluded patients with kidney/liver/heart disease or GI problems.	A: Celecoxib 200 mg po qd Placebo po bid B: Diclofenac 50 mg po bid Placebo po qd	Paracetamol (Acetaminophen) 500 mg prn	71 yrs Male: 31% Ethnicity: NR	OA of knee: 62% OA of hip: 35% OA of knee and hip: 2% <u>Functional Class:</u> I: 9% II: 81% III: 10%	925

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Dahlberg 2009 Scandinavia (Good)	366/9/916	Celecoxib vs Diclofenac PGA of Arthritis (Good or Very Good): Baseline: 11% vs 14% End of Study: 36% vs 36% Physician Global Assessment of Arthritis (Good or Very Good): Baseline: 19% vs 19% End of Study: 45% vs 42% Patient Assessment of Arthritis Pain using VAS: Baseline: 51% vs 49% End of Study: 40% vs 42% Patient Satisfaction Assessment (Pain Relief): Baseline: 5.9 vs 5.8 End of Study: 6.2 vs 6.3 Patient Satisfaction Assessment (Walking/bending): Baseline: 5.0 vs 5.0 End of Study: 6.1 vs 6.0 Physician Satisfaction assessment: Baseline: 5.4 vs 5.2 End of Study: 6.0 vs 5.9

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Dahlberg 2009 Scandinavia (Good)	Celecoxib vs Diclofenac: Total AEs: 19.7% vs 21.2% Death: 1.3% vs 1.1% MI: 0.9% vs 1.3% (although all judged by investigators as to not be related to study medication) Angina: 0.4% vs 1.1% (all judged as not related to study drugs) Heart failure: 0.9% vs 1.1% (1/4 vs 3/5 judged as related to study medication) CVA: 0.2% vs 1.1% GI hemorrhage: 0.2% vs 0% (hemorrhage judged to be related to study drug) Ulcer: 0.2% vs 0.6% (1/1 vs 2/3 ulcers judged to be study drug related) Total CV+Renal: 70 (15.3%) vs 95 (20.7%) Total GI: 7 (1.5%) vs 10 (2.2%) Total Hepatic: 10 (2.2%) vs 39 (8.5)	Celecoxib vs Diclofenac: Total: 181 (39.5%) vs 185 (40.4%) Due to AE: 117 (25.3%) vs 127 (27.5%)	Pfizer sponsored; Authors received a consulting fee from Pfizer; Pfizer provided expert review	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Dentali 2006 Canada	Patients aged >18 yrs receiving long-term warfarin therapy (at least 3 months with a dose administered to achieve a target INR of 2.0–3.0 or 2.5–3.5), with stable anticoagulation, and a diagnosis of OA of the knee, hand, hip, or spine for ≥ 3 months, requiring an NSAID or a non-NSAID analgesic treatment for at least 10 weeks.	A: Celecoxib 200 mg daily B: Codeine phosphate 7–15 mg tid or qd (titrated until pain was controlled) For 5 weeks per phase (crossover)	Warfarin therapy No concomitant antiinflammatory or other analgesic treatment was allowed.	70 years Male: 53% Ethnicity: NR	Mean baseline INR: 2.43 <u>Reason for anticoagulation:</u> Atrial fibrillation: 67% Venous thromboembolic disease: 13% Mechanical valves: 13% Myocardial infarction: 7% <u>Concomitant disease:</u> Previous stroke: 20% Hypertension: 47% Coronary heart disease: 27%	15

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Dentali 2006 Canada	5/0/15	Mean INR values: NSD (mean difference [95% CI] 0.10 [–0.04 to 0.24]; p=0.16) Insufficient evidence to reject the hypothesis that the two treatments had an equal effect on the INR (mean difference [95% CI] 0.10 [–0.04 to 0.24]; p=0.16) based on mean imputation. Excessive anticoagulation: 1 patient during treatment with celecoxib (INR 4.9)

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Dentali 2006 Canada	During treatment with Celecoxib vs Codeine Cardiac arrest due to a myocardial infarction: 0 (0%) vs 1 (6.7%) Dyspepsia: 1 (6.7%) vs (0%) Constipation: 0 (0%) vs 1 (6.7%) Excessive anticoagulation: 1 (6.7%) vs 0 (0%)	Celecoxib vs Codeine Total: 5 (33%) Due to AE: 2 (13.3%) vs 2 (13.3%)	NR	Crossover trial

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Dreiser 1993 France	Men and women 40-80 years treated with femorotibial and/or femoropatellar gonarthrosis diagnosed radiologically.	A: DHEP containing 180 mg of active drug each B: Placebo for 15 days	Paracetamol 500 mg capsules	65.8 years Male: 22.6% Ethnicity: NR	Mean weight male: 73.2 kg Mean weight female: 66.9 kg Mean height male: 170.5 cm Mean height female: 159.8 cm Gonarthrosis type Femoropatellar: 19.4% Femorotibial: 41.3% Both: 38.1% Unknown: 1.3%	155
Emery 2008 UK (Poor)	Men and women ≥45 years with OA of hip requiring joint replacement. Excluded patients with GI problems.	A: Celecoxib 200 mg po qd Placebo B: Diclofenac 50 mg po tid Placebo	Acetaminophen at a max dose of 4 g as a rescue medication	64 years Male: 54% White: 99%	Previous NSAID use: 65%	249

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Dreiser 1993 France	13/NR/unclear	DHEP patch vs placebo, p-value between groups Huskinsson's visual analogue scale values, evolution day 0-15, mean (S.E.): 33.7 (2.1) vs 22.4 (2.2), p<0.002 Change in Lequesne's index values at day 15: 5.0 (0.5) vs -2.8 (0.4), p<0.001 Change in patient's self evaluation at day 15: 1.16 (0.11) vs 0.59 (0.10), p<0.001 Mean nocturnal awakenings during 15 days of trial: 9.8 vs 23.3 (p<0.05) Global judgment of efficacy By the Investigator: Good or Excellent: 64% vs 23% (p<0.001) By the patient: Good or Excellent: 71% vs 27% (p<0.0001)
Emery 2008 UK (Poor)	99/not clear, however, 29 (11.6%) "defaulted"/235	Celecoxib vs Diclofenac: Difference in change in Patients' assessment of arthritis pain by VAS from baseline to week 6 between Celecoxib vs Diclofenac: 12.1 mm favoring Diclofenac Difference in change in Patients' assessment of arthritis pain by VAS from baseline to week 12 between Celecoxib vs Diclofenac: 10.0 mm favoring Diclofenac Pain Satisfaction Scale ("relieve pain quickly enough"): At week 6: 25.4% vs 36.8% (p≤0.041) At week 12: 22.0% vs 41.0% (p=0.011) Improved daily performance week 6: 27.1% vs 40.2% (p=0.021) Better relationship with others week 6: 21.2% vs 30.8% (p=0.043)

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Dreiser 1993 France	DHEP vs Placebo Total subjects with AE: 1 (1.3%) vs 4(5.2%) Edema: 0 vs 1 (1.3%) Nausea and vomiting: 0 vs 1 (1.3%) Slight intermittent itching or burning sensation: 1 (1.3%) vs 2 (2.6%) Global judgment of tolerability By the investigator Good or excellent (n): 67 vs 72 By the patient Good or excellent (n): 77 vs 69	DHEP vs Placebo Total: 1 vs 12, p<0.0001 Due to AE: 0 vs 1	NR	
Emery 2008 UK (Poor)	Total subjects with adverse events: 133 (53%) Celecoxib vs Diclofenac: 67 (53.6%) vs 66 (53.7%) Serious AEs: 6/8 (4.8-6.4%) vs 1 (0.8%) (Also: 1 MI before any study drug given, 1 Death occurred 1 day after conclusion of post treatment follow-up, 1-2 AEs reported 4 months after withdrawal from study) Diarrhea: 10 (8%) vs 10 (8.1%) Dyspepsia: 8 (6.4%) vs 2 (1.6%) Nausea: 3 (2.4%) vs 4 (3.3%) Upper Abdominal Pain: 2 (1.6%) vs 3 (2.4%) Hypertension: 1 (0.8%) vs 6 (4.9%) Headache: 6 (4.8%) vs 7 (5.7%)	Celecoxib vs Diclofenac: Total: 54 (42.9%) vs 45 (36.6%) Due to AE: 13 (10.3%) vs 18 (14.6%)	Sponsored by Pfizer; Primary author has undertaken clinical trials and provided expert advice for Pfizer and Novartis	noninferiority trial

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Goldstein 2007 U.S. (Good)	Men and women ≥18 years with OA and a clinical indication for low-dose ASA without GI disease, endoscopic ulcer, or a positive CLO-test for *H.pylori.*	A: Celecoxib 200 mg po qd 81 mg or 325 mg ASA qd B: Naproxen 500 mg po bid Lansoprazole 30 mg po qd 81mg or 325 mg ASA qd	Open-label antacids were self-administered not to exceed 12 tablets/24 hours	56.7 years Male: 34.6% White: 72.2% Black: 13.5% Hispanic: 10.5% Asian: 2.2% Other: 1.5%	Low-dose ASA: 81 mg: 88.5% 325 mg: 11.5% Neg *H.pylori* : 96.9% No prior NSAID use for 90 days: 25.7% Alcohol: 46.3% Caffeine: 83.4% Tobacco: 17.4%	1045
Herrera 2007 Venezuela (Fair)	Men and women with OA of the knee (age variable). Major GI, liver, kidney, blood disease were excluded.	A: Diclofenac 100 mg CR po qd B: Diclofenac 50mg IR po bid	Acetaminophen 500 mg rescue medication	61.8 years Male: 11.1% Ethnicity: NR	Weight: 71.3 kg Height: 1.57 m BP systolic: 128.88 mmHg BP diastolic: 80.42 mmHg HTN: 46.8% Diabetes: 5% Hx of pain meds: 87.1%	62

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Goldstein 2007 U.S. (Good)	354/12/1045	Celecoxib vs Naproxen+ Lansoprazole: GDU ulcer: 105 (20.3%) vs 95 (18.0%) Week 12 change in pain scores: -18.2% vs -25% Patients with GI complications by endoscopy: 0 vs 1
Herrera 2007 Venezuela (Fair)	NR/NR/62	Diclo CR vs Diclo IR: Baseline VAS: 62.48 vs 61.39 After 24hr: 40.58 vs 38.28 After 72hr: 31.42 vs 29.72 Day 15: 33.24 vs 24.18 Day 30: 21.64 vs 17.29 WOMAC scores: Baseline Function: 29.23 vs 27.55 Baseline Pain: 7.30 vs 6.74 Baseline Rigidity: 3.13 vs 2.42 Day 15 Function: 18.07 vs 15.55 Day 15 Pain: 4.00 vs 3.65 Day 15 Rigidity: 1.67 vs 1.17 Day 30 Function: 15.44 vs 11.75 Day 30 Pain: 3.44 vs 2.71 Day 30 Rigidity: 1.78 vs 1.07 Change in Total WOMAC score from baseline to day 30: -20.46 vs -22.21 Reported feeling better: 76% vs 94% Clinically improved by physician assessment: 83% vs 97% Needing rescue meds: 26% vs 36%

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Goldstein 2007 U.S. (Good)	Celecoxib vs Naproxen+ Lansoprazole: % of subjects reporting any AE: 53% vs 57% % of subjects reporting serious AE: 1.2% vs 0.8% URI: 9% vs 11% Dyspeptic Sx: 10% vs 7% Diarrhea: 4% vs 7% Abdominal Pain: 6% vs 6% Nausea/Vomiting: 6% vs 6% Palpitations: 0% vs 0.2%	Celecoxib vs Naproxen+ Lansoprazole: Total: 169 (32.8%) vs 185 (35.0%) Due to AE: 33 (6.4%) vs 35 (6.6%)	NR	
Herrera 2007 Venezuela (Fair)	Diclo CR vs Diclo IR: Total AEs: 7 (22.6%) vs 6 (19.4%)	NR; Diclo CR vs Diclo IR: 0 (0%) vs 1 (3.2%)	NR	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Niethard 2005 Germany (Good)	Men and women ≥45 years with clinically diagnosed symptomatic unilateral OA of the knee for at least 6 mos.	A: Diclofenac diethylamine gel 1.16%, 4 g qd B: Placebo for 3 weeks	Acetaminophen 500 mg rescue medication up to 4 tablets per day	66 years Male: 36.5% Caucasian: 100%	Has periarticular pain: 29% Has moderate or severe tenderness pressure Joint space medially: 93% Joint space laterally: 25.4% Patella medially: 40.4% Patella laterally: 14% Has moderate or severe swelling of joint capsule: 27.5% Joint effusion: 14.5% Osteophytes: 99% Sclerosis: 91% Subchondral cysts: 14% Joint space narrowing: 96.5%	238

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Niethard 2005 Germany (Good)	38/NR/327	Diclofenac versus placebo Decline from baseline in pain on movement as measured on VAS averaged over 8-21 days, mean (SD): 14 (16) vs 10 (13), p=0.005 (vs placebo) Decline from baseline in spontaneous pain averaged over 8-21 days, mean, SD: 0.52 (0.55) vs 0.36 (0.54), p=0.02 Pain relief averaged over 8-21 days: 1.51 (0.93) vs 1.34 (0.79), p=0.10 Proportion of patients using any rescue medication overall: 39% vs 39% <u>Study center-based efficacy assessments:</u> Decline from baseline visit in pain intensity, mean (SD), p-value vs placebo Week 1: 18(20) vs 12 (18), p=0.03 Week 2: 27 (23) vs 17 (21), p=0.0002 Week 3: 34 (26) vs 25 (24), p=0.006 Decline from baseline visit in WOMAC pain score, mean (SD) Week 1: 11(14) vs 8 (14), p= 0.22 Week 2: 17 (18) vs 9 (18), p<0.0001 Week 3: 22 (21) vs 14 (23), p=0.0002 Physical function score, mean, (SD), p-value vs placebo Week 1: 11 (13) vs 8 (12), p=0.12 Week 2: 18 (17) vs 11(15), p=0.0002 Week 3: 23 (21) vs 16 (22), p=0.001 Stiffness Score, mean (SD), p value vs placebo Week 1: 11 (18) vs 8 (15), p=0.30 Week 2: 17 (21) vs 11 (20), p=0.002 Week 3: 22 (23) vs 14 (24), p=0.0004 End of study global treatment efficacy: Good, very good or excellent: 69% vs 58%, p=0.03 OARSI/OMERACT response rate at final visit: 62% vs 46%, p=0.01

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Niethard 2005 Germany (Good)	Diclofenac vs placebo 9% vs 9% GI events (dry mouth and nausea): 0 vs 2 Edema: 1 vs 0 Allergic contact dermatitis: 1 vs 1 Application site reactions: 2 vs 2 (placebo patients had application site irritation and inflammation, application site burning) SAE: 0 vs 1 (brain tumor)	Diclofenac versus placebo Total: 15 (12.8%) vs 23 (19%) Due to AE: 2 (1.7) vs 0	Novartis consumer health	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Prabhu 2008 India (Fair)	Males and females >18 years with confirmed diagnosis of OA.	A: Paracetamol 500 mg B: Ibuprofen 400 mg C: Nimesulide 100 mg D: Diclofenac 50 mg E: Nimesulide 100 mg/Racemethionine 50mg For 3 months	NR	NR, except statement that age and weight factors were found to be comparable in all 5 groups	NR	60
Roth 1995 U.S. (Poor)	Included patients were those who provided evidence on i) pain aggravated by motion ii) limitation of movement iii) tenderness on pressure	A: Topical diclofenac gel 2 g qd B: Placebo For 2 weeks	None	67 years Male: 27.7% Caucasian: 96%	Duration of OA: 10.3 years Percentage of patients by sentinel joint: Hand: 24% Foot: 7% Cervical spine: 13% Spine: 1% Lower spine: 27% Knee: 23% Hip: 2% Shoulder: 3%	119

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Prabhu 2008 India (Fair)	0/0/60	Paracetamol vs Ibuprofen vs Nimesulide vs Diclofenac vs Nimesulide/Racemethionine <u>Pain intensity:</u> Change from baseline to final visit was significant at 5% level in all groups (p=0.02) Reduction in pain intensity: 50% vs 49.35% vs 53.85% vs 50.63% vs 53.75% <u>Pain on movement:</u> Reduction was significant at 5% level for all groups over the course of the study (p=0.02) Reduction in pain on movement: 58% vs 63.3% vs 66.6% vs 63.3% vs 66.6% <u>Tenderness:</u> Reduction was significant at 5% level for all groups over the course of the trial (p=0.02) Reduction in tenderness: 95.8% vs 91.3% vs 95.4% vs 82.6% vs 100%
Roth 1995 U.S. (Poor)	7/NR/NR	Diclofenac vs placebo Change from baseline in patient assessment of OA pain at week 2: -0.7 (1.0) vs -0.4 (0.9), p=0.0568

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Prabhu 2008 India (Fair)	NR	None	NR	
Roth 1995 U.S. (Poor)	Diclofenac vs placebo Pruritus: 7 vs 15 Rash: 5 vs 11	Diclofenac vs placebo Total: 3 (5.08%) vs 4 (6.7%) Due to AE: NR	NR	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Roth 2004 U.S. and Canada (Fair)	Men and non-pregnant women aged 40 to 85 years with primary OA of the knee.	A: Topical diclofenac solution 1.5% B: Placebo For 12 weeks	Rescue analgesia with acetaminophen 325 mg X4 (max) tablets/day. Aspirin ≤325 mg/day permitted for cardiovascular prophylaxis.	64.1 years Male: 32.2% White: 89% Oriental: 0.3% Black: 9.2% Hispanic: 1.5%	Weight: 91 kg Height: 166.8 cm	326

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Roth 2004 U.S. and Canada (Fair)	98/3/320	Diclofenac vs Placebo Change from baseline in WOMAC pain, mean, (SD): -5.9 (4.7) vs -4.3 (4.4); p<0.005 vs diclofenac, % change -45.7% vs -33.3% Change from baseline in WOMAC physical function, mean, (SD): -15.4(15.3) vs -10.1 (13.9), p<0.005 vs diclofenac, % change-36.7% vs -24.5% Change from baseline in WOMAC stiffness, mean, (SD): -1.8 (2.1) vs -1.3 (2.0), p<0.005 vs diclofenac, % change -35.1% vs -24.1% Change from baseline in PGA, mean, (SD): -1.3 (1.2) vs -0.9 (1.2), p<0.005 vs diclofenac, % change-42.2 vs -30.4% Mean (SD) Pain on walking score change from baseline -1.18 (1.11) vs -0.87 (1.06), p<0.005 vs diclofenac, % change -45.0 % vs -32.7%

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Roth 2004 U.S. and Canada (Fair)	Diclofenac vs placebo Incidence of AE in GI tract: 12% vs 9% (p=0.49) AE related to renal system: 0% vs 0% <u>GI tract infections</u> Abdominal pain: 3.0% vs 1.9% Constipation: 1.2% vs 0.6% Diarrhea: 0% vs 1.9% Dyspepsia: 4.9% vs 3.7% Flatulence: 2.4% vs 1.2% Melena: 0% vs 1.2% Nausea: 2.4% vs 0.6% Vomiting: 0.6% vs 0% <u>Others</u> Asthma: 1.8% vs 0.6% Dizziness: 1.2% vs 0% Edema: 2.4% vs 1.2% Headache: 5.5% vs 4.3% Halitosis: 0% vs 1.2% Taste perversion: 1.8% vs 3.1%	Diclofenac vs placebo Total: 45 (27.4%) vs 53 (32.7%) Due to AE: 8 (4.9%) vs (2.5%)	Dimethaid Healthcare Ltd.	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Sieper, 2008 Germany (Fair)	Male/Female 18-75 years AS, presence of axial involvement, no peripheral involvement and need of NSAID daily. Acute episode of moderate to severe pain at baseline or increase in pain from screening visit. Previous episodes of inflammatory bowel disease or GI ulcers within previous year and confirmed by endoscopy	A. Celecoxib 200mg po qd B. Celecoxib 200mg po bid C. Diclofenac SR 75 mg bid	Proton pump inhibitors; disease modifying antirheumatic drugs if stable dose for 3 months and no planned changes during study period; Prednisolone ≤10mg/day	44.8 years Male: 69% NR	NR	458

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Sieper, 2008 Germany (Fair)	77/8/373	Celecoxib 200 mg qd vs Celecoxib 200 mg bid vs Diclofenac 75 mg bid VAS pain (0–100 mm) Mean change from baseline (SD): -28.2 (27.2) vs -29.8 (25.1) vs -30.8 (25.6) LS mean treatment contrast (SD): 2.9 (2.7) vs 2.1 (2.8) vs NA 95% CI for the treatment contrast: -2.4 to 8.2 vs -3.3 to 7.6 vs NA BASDAI (0–10), mean (SD): Mean change from baseline: -0.99 (2.11) vs -1.32 (1.72) vs -1.48 (1.76) LS mean treatment contrast: 0.42 (0.20) vs 0.11 (0.20) vs NA 95% CI for the treatment contrast: 0.03 to 0.81 vs -0.29 to 0.51 vs NA BASFI (0–10), mean (SD): Mean change from baseline: -0.8 (2.0) vs -0.9 (1.5) vs -0.9 (1.8) LS mean treatment contrast: 0.1 (0.2) vs -0.0 (0.2) vs NA 95% CI for the treatment contrast: -0.3 to 0.5 vs -0.4 to 0.3 vs NA Global Assessment disease activity, subjects (0–10), mean (SD): Mean change: -2.0 (2.7) vs -2.2 (2.5) vs -2.3 (2.6) LS mean treatment contrast: 0.3 (0.3) vs 0.3 (0.3) vs NA 95% CI for the treatment contrast: -0.2 to 0.8 vs -0.2 to 0.8 vs NA BASMI (0–10), mean (SD): Mean change: -0.3 (1.4) vs -0.3 (1.4) vs -0.5 (1.3) LS mean treatment contrast: 0.1 (0.1) vs 0.1 (0.1) vs NA 95% CI for the treatment contrast: -0.1 to 0.4 vs -0.1 to 0.4 vs NA

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Sieper, 2008 Germany (Fair)	Celecoxib 200 mg qd vs Celecoxib 200 mg bid vs Diclofenac 75 mg bid Any AEs: 92 (60.1%) vs 68 (45.3%) vs 91 (58.7%) Drug-related AEs 29 (19.0%) vs 31 (20.7%) vs 41 (26.5%) Subjects with drug-related serious AEs: 1 (0.7%) vs 0 vs 0 Gastrointestinal AEs: 23 (15.0%) vs 25 (16.7%) vs 44 (28.4%) Upper GI AEs: 10 (6.5%) vs 11 (7.3%) vs 28 (18.1%) Lower GI AEs: 9 (5.9%) vs 5 (3.3%) vs 20 (12.9%) Abdominal distension: 3 (2.0%) vs 0 vs 1 (0.6%) Abdominal pain (not otherwise specified): 1 (0.7%) vs 1 (0.7%) vs 4 (2.6%) Abdominal pain upper: 5 (3.3%) vs 5 (3.3%) vs 14 (9.0%) Diarrhea (not otherwise specified): 6 (3.9%) vs 4 (2.7%) vs 15 (9.7%) Epigastric discomfort: 0 vs 1 (0.7%) vs 6 (3.9%) Gastritis (not otherwise specified): 1 (0.7%) vs 4 (2.7%) vs 2 (1.3%) Nausea: 0 vs 2 (1.3%) vs 5 (3.2%) Stomach discomfort: 4 (2.6%) vs 1 (0.7%) vs 4 (2.6%) Influenza-like illness: 8 (5.2%) vs 4 (2.7%) vs 2 (1.3%) ALT increased: 0 vs 0 vs 6 (3.9%) Arthralgia: 2 (1.3%) vs 3 (2.0%)vs 0 AS aggravated: 6 (3.9%) vs 5 (3.3%) vs 2 (1.3%) Headache: 30 (19.6%) vs 22 (14.7%) vs 34 (21.9%) Nasopharyngitis: 5 (3.3%) vs 5 (3.3%) vs 4 (2.6%) Pharyngitis: 5 (3.3%) vs 1 (0.7%) vs 0	77; 35 (8 Celecoxib 200 mg qd, 12 Celecoxib 200 mg bid, 15 Diclofenac 75 mg bid)	Pfizer	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Simon, 2009 U.S.and Canada (Fair)	Male/Female 40-85 years old with primary OA of knee based on: standard radiographic criteria for OA on xray within 3 months; pain with regular use of NSAID, flare of pain and minimum Likert pain score of 8 at baseline following washout	A. Topical diclofenac solution 1.5% (Tdiclo) B. DMSO vehicle C. Placebo D. Oral doclofenac (Odiclo) 100 mg E. Topical diclofenac and oral diclofenac	Stable treatment with glucosamine, chondroitin, anti-depressants, proton pump inhibitors for previous 90 days or 325mg acetylsalicylic acid previous 30 days; acetaminophen up to 4 per day except for 3 days prior to assessment	61.5 years Male: 37.8% Caucasian: 77.5% Black: 5.3 % Hispanic: 5.7 % Asian: 9.1% Other: 2.3%	Patients with bilateral disease: 95% Hypertension: 3.2% Normal BMI: 11.14% Overweight: 29% Obese: 58.7%	775

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Simon, 2009 U.S.and Canada (Fair)	248/13/772	Topical diclofenac vs placebo vs DMSO vs Oral Diclofenac vs Topical diclofenac/oral diclofenac WOMAC Pain, mean change in score: -6.0 (p=0.025 vs placebo, p=0.009 vs DMSO) vs -4.7 vs -4.7 vs -6.4 vs -7.0 WOMAC Physical Function, mean change in score: 15.8 (p=0.034 vs placebo, p=0.026 vs DMSO) vs 12.3 vs 12.1 vs 17.5 vs 18.7 Patient overall health assessment: mean change in score: 0.95 (p<0.0001 vs placebo, p=0.016 vs DMSO) vs 0.37 vs 0.65 vs 0.88 vs 0.95 PGA, mean change in score: 1.36 (p=0.016 vs placebo, p=0.018 vs DMSO) vs 1.01 vs 1.07 vs 1.42 vs 1.53 WOMAC Stiffness, mean change in score: 1.93 (p=0.035 vs DMSO) vs 1.52 vs 1.48 vs 2.07 vs 2.30

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Simon, 2009 U.S.and Canada (Fair)	Topical diclofenac vs placebo vs DMSO vs Oral Diclofenac vs Topical diclofenac/oral diclofenac Any AE: 96 (62.3%) vs 90 (57.3%) vs 97 (60.2%) vs 94 (62.3%) vs 98 (64.5%) Any digestive system event: 10 (6.5%) vs 15 (9.6%) vs 18 (11.2%) vs 36 (23.8%) vs 39 (25.7%) Abdominal pain: 5 (3.2%) vs 1 (0.6%) vs 5 (3.1%) vs 11 (7.3%) vs 3 (2.0%) Dyspepsia: 4 (2.6%) vs 6 (3.8%) vs 6 (3.7%) vs 6 (4.0%) vs 5 (3.3%) Diarrhea: 2 (1.3%) vs 3 (1.9%) vs 2 (1.2%) vs 7 (4.6%) vs 12 (7.9%) Liver function tests abnormal: 3 (1.9%) vs 1 (0.6%) vs 6 (3.7%) vs 12 (7.9%) vs 11 (7.2%) Rectal hemorrhage: 1 (0.6%) vs 0 vs 0 vs 0 vs 5 (3.3%) Nausea: 0 vs 0 vs 1 (0.6%) vs 3 (2.0%) vs 5 (3.3%) Any skin/appendages event: 41 (26.6%) vs 12 (7.6%) vs 27 (16.8%) vs 11 (7.3%) vs 47 (30.9%) Headache: 27 (17.5%) vs 18 (11.5%) vs 21 (13.0%) vs 26 (17.2%) vs 21 (13.8%) Back pain: 15 (9.7%) vs 10 (6.4%) vs 15 (9.3%) vs 11 (7.3%) vs 4 (2.6%) Arthralgia: 14 (9.1%) vs 15 (9.6%) vs 25 (15.5%) vs 12 (7.9%) vs 7 (4.6%) Pain: 7 (4.5%) vs 5 (3.2%) vs 11 (6.8%) vs 8 (5.3%) vs 1 (0.7%) Respiratory disorder: 5 (3.2%) vs 6 (3.8%) vs 4 (2.5%) vs 8 (5.3%) vs 7 (4.6%) Conjunctivitis: 4 (2.6%) vs 1 (0.6%) vs 0 vs 3 (2.0%) vs 0	Topical diclofenac vs placebo vs DMSO vs Oral Diclofenac vs Topical diclofenac/oral diclofenac Total: 51 (33.1%) vs 54 (34.4%) vs 48 (29.8%) vs 44 (29.1%) vs 51 (33.6%) Due to AE: 16 (10.4%) vs 18 (11.5%) vs 12 (7.5%) vs 19 (12.6%) vs 23 (15.1%)	Nuvo research	

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Tugwell 2004 Canada (Fair)	Men and non pregnant women 40-85 years old, with symptomatic primary OA of the knee and a recent (within 3 mos) radiographic examination showing OA.	A: Topical Diclofenac solution+oral placebo B: Placebo topical solution+oral 50 mg tid diclofenac capsules For 12 weeks	NR	64 years Male: 43% White: 94.1% Oriental: 0.8% Black: 1.1% Hispanic: 0.2% Other: 3.9%	Weight: 88 kg Height: 166 cm Heart rate: 74.5 bpm	622

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Tugwell 2004 Canada (Fair)	245/10/604	Topical vs oral diclofenac Mean (SD) Change in WOMAC pain score (mm): -118 (121) vs -134 (127), % improvement: 41% vs 46% , p=0.10 (between treatment groups) Mean (SD) Change in WOMAC physical function (mm): -348 (400) vs -438 (426), % improvement: 36% vs 45%, p=0.008 (between treatment groups) Mean (SD) Change in WOMAC stiffness score (mm): -45 (58) vs -52 (61), % improvement: 37% vs 42%, p=0.14 (between treatment groups) Mean (SD) change in PGA score: -27 (31) vs -32 (32), % improvement: 39% vs 46%, p=0.08 (between treatment groups) Pain on walking, difference in mean change score: 1.7 mm (95% CI, -2.9 to 6.4) % of responders to treatment according to OMERACT-OARSI criteria: 66% vs 70%, p=0.37 (between treatment groups)

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Tugwell 2004 Canada (Fair)	Topical diclofenac vs Placebo All GI events: 35% vs 48%, p=0.0006 Abdominal pain: 12% vs 22%, p=0.0008 Constipation: 8% vs 10%, p=0.40 Diarrhea: 9% vs 7%, p=0.001 Dyspepsia: 15% vs 26%, p=0.001 Flatulence: 15% vs 26%, p=0.001 Melena: 1% vs 2%, p=0.36 Nausea: 8% vs 13%, p=0.04 Vomiting: 2% vs 2%, p=0.56 Other Asthma: 0.6% vs 3%, p=0.02 Dizziness: 0.6% vs 4%, p=0.002 Dyspnea: 0% vs 2%, p=0.01 Edema: 7% vs 8%, p=0.65 Halitosis: 1% vs 0.3%, p=0.37 Headache: 5% vs 6%, p=0.29 Hypertension: 1% vs 2%, p=0.20 Pharyngitis: 4% vs 0.6%,p=0.004 Taste perversion: 2% vs 0.6%, p=0.29 Patients with clinically significant elevation of AST: 0.4% vs 1.4% Patients with clinically significant elevation of ALT: 1.1% vs 4.7% Mean (SD)Change from baseline in AST(U/l): 0.2 (8) vs 5.7 (23), p=0.0002 Mean (SD) Change from baseline in ALT(U/l):1.2 (15) vs 15 (60), p=0.0003 Patients changing from normal to abnormal AST: 2% vs 10%, p=0.0001 Patients changing from normal to abnormal ALT: 5% vs 17%, p<0.0001	Topical vs oral diclofenac Total: 129 (41.5%) vs 116 (37.3%) Due to AE: 64 (21%)vs 79 (25.4%)	Dimethaid Healthcare Ltd.	equivalence study

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Wagenitz 2007 Germany (Good)	Men and women 18-75 years with OA of hip and/or knee with functional class I-III with no major GI, heart, kidney, or liver disease.	A: Diclofenac 100 mg SR-CAP po B: Diclofenac 100 mg SR-TAB po	Low dose aspirin; Paracetamol rescue medication	62.3 years Male: 34% Ethnicity: NR	Weight: 82.4 kg Height: 166.9 cm OA multiple joints: 88.5% OA localized: 17.7%	209

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Wagenitz 2007 Germany (Good)	38/NR/209	SR-CAP vs SR-TAB: At rest: Baseline: 64.8 vs 63.8; change from baseline: Day 7: 37.4 vs 37.6 Change from baseline: 26.8 vs 26.1 Day 14: 21.2 vs 27.7 Change from baseline: 43.7 vs 36.6 With movement: Baseline: 73.1 vs 70.6 Day 7: 45.8 vs 43.5 Change from baseline: 27.3 vs 27.1 Day 14: 31.1 vs 34.1 Change from baseline: 42.5 vs 36.4 Patient Global efficacy: 92.1% vs 86.6% Investigator Global efficacy: 91.0% vs 89.0% Patient Assessment of Tolerability good or very good: 85.4% vs 78.1% Investigator Assessment of tolerability as poor: 1.1% vs 9.8%

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wagenitz 2007 Germany (Good)	SR-CAP vs SR-TAB: Percent of subjects with ≥ 1 AE: 30.8% vs 39% Percent with GI tract AE: 25.0% vs 32.4% Percent with serious AE: 1% vs 1%	SR-CAP vs SR-TAB Total withdrawals not reported by treatment group; 20 subjects withdrew due to AE: 8 (7.7%) vs 12 (11.4%)	Funded by Maepha Ltd, Aesch, Switzerland who also provided the study medications	Noninferiority study

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N (Number randomized)
Whelton, 2006 US and Canada companion to CLASS	Outpatients ≥18 years of age diagnosed with RA or OA evident for ≥3 months that required continuous treatment with an NSAID for the duration of the trial. Excluded patients with significant renal disease or dysfunction.	Group A: Celecoxib 400 mg bid Group B: Ibuprofen 800 mg tid Group C: Diclofenac 75 mg bid For >180 days	Use of stable doses of aspirin up to 325 mg daily, antihypertensive and diuretic medications	60.2 yrs % Male: 68.8% Ethnicity: NR	History of hypertension: 38.8% History of diabetes: 8.3% Mean blood pressure: 133/80 mmHg Creatinine serum level (mg/dl): 0.79 Creatinine clearance (ml/min): 113.2	8059

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Number withdrawn/ lost to fu/analyzed	Efficacy/Effectiveness outcomes
Whelton, 2006 US and Canada companion to CLASS	4559/0/7968	Celecoxib vs diclofenac vs ibuprofen <u>Blood pressure effects:</u> New-onset hypertension: 2% vs 2% vs 3.1% (P<0.05) Aggravated hypertension: 0.8% vs 0.6% vs 1.2% Mean change in blood pressure (systolic/diastolic): -0.6/-0.7 mmHg vs -0.8/-1.1 mmHg vs 0.3/-0.6 mmHg Percent of patients with increases in systolic blood pressure (>20 mmHg from baseline and absolute value >140 mmHg): 5.0% vs 6.6% (p<0.05) vs 7.0% (p<0.05) Percent of patients with increases in diastolic blood pressure (>15 mmHg from baseline and absolute value >90 mmHg): 1.9 vs 1.2 vs 2.2 <u>Renal Function:</u> Mean change in serum creatinine (mg/dl): 0.009 vs 0.027 (p<0.05) vs 0.017 Mean change in estimated creatinine clearance (ml/min): 0.08 vs -2.82 (p<0.05) vs -0.96 Incidence of ≥30% reductions in estimated creatinine clearance from baseline was significantly lower in patients treated with celecoxib as compared with diclofenac. Clinically important reductions in renal function in patients with mild prerenal azotemia: 3.7% vs 7.3% (p<0.05) vs 7.3% (p<0.05)

Evidence Table 1. Data abstraction of randomized controlled trials

Author Year Country Trial name (Quality rating)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Whelton, 2006 US and Canada companion to CLASS	Celecoxib vs diclofenac vs ibuprofen Withdrawals for hypertension-related adverse events: 0.3% vs 0.2% vs 0.3% Any edema-related adverse event: 4.1% vs 4.1% vs 6.2% (p<0.05) Congestive heart failure: 0.3% vs 0.2% vs 0.5% Increase in body weight of ≥3%: 20.7% vs 17.6% vs 21.1% Uremia: 0 (0%) vs 0 (0%) vs 1 (0.05%) Hyponatremia: 2 (0.05%) vs 0 (0%) vs 1 (0.05%)	Celecoxib vs diclofenac vs ibuprofen Total: 2208 (55.4%) vs 1057 (53%) vs 1294 (65.2%) Due to AE: 905 (22.7%) vs 540 (27.1%) vs 461 (23.2%)	NR	

Evidence Table 2. Quality assessment of randomized controlled trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Altman 2009	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Baer 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Barkhuizen 2006	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Barthel 2009	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Bookman 2004	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Chan 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chan 2010 (CONDOR)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dahlberg 2009	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Dentali 2006	Yes	Yes	Unclear; baseline characteristics not compared based on order of randomization	Yes	Yes	Yes	Yes
Emery,2007	Yes	Unclear	No. Statistics not given for randomized	Yes	Unclear	Yes	Yes
Goldstein, 2007	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes

Evidence Table 2. Quality assessment of randomized controlled trials

Author, Year Country	Intention-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
Altman 2009	Yes	Yes	Unclear, Unclear, Unclear	Yes, Yes	Fair
Baer 2005	Yes, only excluded 4/216 (2%)	Yes	Unclear, Yes, Unclear	Overall=No (28%) Between-group=Yes	Fair
Barkhuizen 2006	Unclear; analyses performed on patients who took ≥ dose of study	Unclear	Unclear, Unclear, Unclear	No; 33% overall Yes; celecoxib 200 mg=27%, celecoxib 400	Fair
Barthel 2009	Yes, only excluded 1/492 (0.2%)	Yes	Unclear, Yes, Unclear	Yes, Yes	Fair
Bookman 2004	Yes; only excluded 1/248 (0.4%)	Yes	Unclear, Yes, Unclear	Yes, Yes	Fair
Chan 2007	Yes	Yes	Unclear, Yes, Yes	Yes, Yes	Good
Chan 2010 (CONDOR)	Yes	Yes	Unclear, Unclear, Unclear	Yes, Yes	Good
Dahlberg 2009	Yes, for primary outcome and AEs; No, for other comparisons	Yes	Unclear, Unclear, Unclear	Yes-although attrition high, subjects were elderly and duration of study was 1 year; Yes-similar attrition in both groups	Fair
Dentali 2006	Yes	yes	Unclear, Yes, Unclear	No, Unclear Overall=4/26 (27%) Between-group=Group assignment not reported for 2 withdrawals	Fair
Emery,2007	No. 5.6% of subjects not analyzed in "modified	Do not know that they were similar at	Unclear,unclear,unclear	No-40% loss in 12 week study. Yes, similar	Poor
Goldstein, 2007	Yes	Yes	Unclear,adherence,unclear	Yes, Yes	Fair

Evidence Table 2. Quality assessment of randomized controlled trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Herrera, 2007	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Niethard 2005	Yes	Yes	Yes, for the most part, Diclofenac patients have	Yes	Yes	Yes	Yes
Prabhu 2008	Unclear	Unclear	Unclear	Yes	Unclear	No	No
Roth 1995	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Roth 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sieper 2008	Unclear	Unclear	Unclear, not shown	Yes	Unclear	Yes; double-dummy	Yes; double-dummy
Simon 2009	Yes	Yes	Yes	Yes	Unclear	Yes; double dummy	Yes; double dummy
Tugwell 2004	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Wagenitz, 2007	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes

Evidence Table 2. Quality assessment of randomized controlled trials

Author, Year Country	Intention-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
Herrera, 2007	Yes	Yes	Unclear,unclear,unclear	Yes, Yes	Fair
Niethard 2005	Yes	Yes	Unclear, Unclear, Unclear	Yes, Yes	Good
Prabhu 2008	Yes	Yes	Unclear, Unclear, Unclear	Unclear, Unclear	Fair
Roth 1995	Unclear	Unclear	Unclear, Unclear, Unclear	Yes, Yes	Poor
Roth 2004	Yes, only excluded 4/326 (1.2%)	Yes	Unclear, Yes, Unclear	Overall=No, 30% Differential=Yes	Fair
Sieper 2008	Yes; only excluded 4/458 (0.9%) from "full analysis set"	Yes	Unclear, Unclear, Unclear	Yes; 77/458 (16.8%) overall Yes	Fair
Simon 2009	Yes; only excluded 0.4%	Yes	Unclear,Yes-89%,Unclear	Overall=No, 32% Differential=Yes	Fair
Tugwell 2004	Yes; only excluded 18/622 (3%)	Yes	Unclear, Yes, Unclear	Overall=No, 39% Differential=Yes	Fair
Wagenitz, 2007	Yes	Yes	Unclear,unclear,unclear	Yes, Yes	Fair

Evidence Table 3. Data abstraction of observational studies

Author, year Country	Study design	Time period covered, data source	Sample size	Population characteristics	Results
Rahme 2007	Retrospective cohort	Government of Quebec health services administrative databases between April 1999 and December 2002	Celecoxib=141,575 Celecoxib plus PPI=25,982 Nonselective NSAID=144,959 Nonselective NSAID plus PPI=19,975	Mean age=74.2 years 63% female Race NR 22% osteoarthritis 3% rheumatoid arthritis	Association between drug exposure and gastrointestinal hospitalization, adjusted hazard ratio (95% CI): Celecoxib=1 (reference) Celecoxib plus PPI: Overall=0.69 (0.52 to 0.93); Age <75 years=0.98 (0.63 to 1.52); Age ≥ 75 years=0.56 (0.38 to 0.81) Nonselective NSAID: Overall=2.18 (1.82 to 2.61); Age <75 years=1.94 (1.46 to 2.58); Age ≥ 75 years=2.38 (1.89 to 3.00) Nonselective NSAID plus PPI: Overall=0.98 (0.67 to 1.45); Age < 75 years=0.96 (0.52 to 1.76); Age ≥ 75 years=1.00 (0.61 to 1.64)
Solomon 2008 Pennsylvania	Retrospective cohort	Prescription (Pharmaceutical Assistance Contract for the Elderly in Pennsylvania) and healthcare (Medicare) claims data during the years 1999-2004	Overall: Celecoxib=40,865 Diclofenac=4,141 Ibuprofen=11,796 Naproxen=10,228 Other NSAIDs=26,849 NR for subgroup of patients age ≥ 80 years	Mean age=80 years 84% female 93% white 1.8% rheumatoid arthritis 17% osteoarthritis	Cardiovascular disease event rates (95% CI) for subgroup of patients age ≥ 80 years: Celecoxib=13.5% (12.7% to 14.3%) Diclofenac=12.5% (9.3% to 16.4%) Ibuprofen=17.8% (14.9% to 21.0%) Naproxen=12.8% (10.4% to 15.7%) Other NSAIDs=13.4% (12.0% to 15.0%)
Turajane 2009 Thailand	Retrospective cohort	Police General Hospital's hospitalization records and dispensing database from July 2004 to June 2007	1,030 patients with 12,591 prescriptions: NSAIDs: 3,982 prescriptions; celecoxib=4,426, etoricoxib=4,183	Mean age=69.6 years 74% female 100% Thai 100% osteoarthritis	Cardiovascular events (all myocardial infarction subtypes and heart failure):celecoxib compared with NSAIDs=adjusted OR 0.37, 95% CI NR, *P*= 0.40

Evidence Table 3. Data abstraction of observational studies

Author, year Country	Study design	Time period covered, data source	Sample size	Population characteristics	Results
Vestergaard 2006 Denmark	Case control	Danish National Hospital Discharge Register between 1/1/2000 to 12/31/2000	Cases=124,655 Controls=373,962	Mean age=43 52% female Race NR 1.7% rheumatoid arthritis 4.8% osteoarthritis	Risk of fracture associated with use ≤ year ago: Adjusted OR (95% CI) Celecoxib=0.94 (0.84 to 1.04) Diclofenac=1.39 (1.35 to 1.44) Diflunisal=1.13 (0.85-1.50) Etodolac=1.14 (1.06 to 1.22) Ibuprofen=1.76 (1.72 to 1.81) Indomethacin=1.22 (1.09 to 1.38) Ketoprofen=1.17 (1.04 to 1.32) Meloxicam=1.03 (0.85 to 1.26) Nabumetone=1.16 (0.99 to 1.36) Naproxen=1.37 (1.29 to 1.46) Piroxicam=1.19 (1.09 to 1.30) Sulindac=0.73 (0.43 to 1.24) Tenoxicam=1.32 (1.14 to 1.54) Tiprofenic acid=0.87 (0.72 to 1.06)

Evidence Table 4. Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Rahme 2007	Yes	No	Yes	Yes
Solomon 2008 United States	Yes	Yes for primary, unclear for secondary analysis	Yes	Yes
Turajane 2009 Thailand	Yes	No	Yes	Yes
Vestergaard 2006 Denmark	Yes	No	Unclear; Fracture types not specified.	Unclear; specific ICD-10 codes used to identify fractures not reported. Data for drug exposure does not contain OTC products.

Evidence Table 4. Quality assessment of observational studies

Author Year Country	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Rahme 2007	Yes	Unclear. Did not control for nonprescription use of nonselective NSAIDs, aspirin, or gastroprotective agents, or duration of index study drug use prior to the study period.	Yes	Fair
Solomon 2008 United States	Yes	Unclear. Did not look at warfarin use, and analysis on ASA is not clear.	Yes	Fair
Turajane 2009 Thailand	No, determination of association between NSAIDs and events entirely relied on the considered opinion of the treating physician and their team, blinding NR	Yes	Yes	Fair
Vestergaard 2006 Denmark	Yes	Yes	Yes	Fair

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs
Chen, 2006	To evaluate the risk of cerebrovascular events with cox-2 inhibitors	1966-2006	DB RCTs of at least 4 weeks duration comparing any individual coxib against placebo or another active ingredient and reported on the proportion of patients experiencing cerebrovascular events	88116 patients	Double blind RCTs of 4 weeks duration
Chen, 2007	Evaluate the risk of myocardial infarction associated with selective cox-2 inhibitors	1966-2006	DB RCTs of at least 4 weeks duration comparing coxib against placebo or an active treatment and reported on the proportion of patients experiencing myocardial infarction	99087 patients	Double blind RCTs of 4 weeks duration

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(6) Characteristics of identified articles: populations	(7) Characteristics of identified articles: interventions	(8) Main results
Chen, 2006	OA: 22 trials RA: 8 trials OA or RA: 2 trials Chronic lower back pain: 1 trial Colorectal adenomas: 3 trials Mild cognitive impairment or early Alzheimer's disease: 4 trials	Celecoxib, rofecoxib, etoricoxib, valdecoxib, lumiracoxib, diclofenac, ibuprofen, naproxen, nabumetone, paracetamol, loxoprofen	NR (see adverse events)
Chen, 2007	OA 27 trials RA: 14 trials OA or RA: 4 trials Ankylosing spondylitis: 1 trial Chronic low back pain: 1 trial Colorectal adenomas: 3 trials Mild cognitive impairment or early Alzheimer's disease: 4 trials	celecoxib, rofecoxib, etoricoxib, valdecoxib, lumiracoxib, diclofenac, ibuprofen, naproxen, nabumetone, paracetamol, loxoprofen	NR (see adverse events)

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Chen, 2006	NR	Risk of any cerebrovascular events Celecoxib vs placebo Event/Number: 24/2574 vs 12/1447, OR 1.11 (95% CI, 0.55 to 2.24), Test for heterogeneity: x^2=0.12, d.f=2, p=0.94, I^2=0% Celecoxib vs any NSAID Event/Number: 19/14430 vs 27/9547, OR 0.53 (95% CI, 0.28 to 1.02), Test for heterogeneity x^2=5.86, d.f.=5, p=0.32, I^2=14.6% Celecoxib vs naproxen :Event/number: 14/9784 vs 4/1399, Pooled OR 0.49 (95% CI, 0.14 to 1.78), Test for heterogeneity: p=0.47, I^2=0.00% Celecoxib vs diclofenac: Event/number: 19/13496 vs 17/6163, Pooled OR 0.58 (95% CI, 0.27 to 1.24), Test for heterogeneity: p=0.21, I^2=0.34% Celecoxib vs ibuprofen: Event/Number: 4/3987 vs 6/1985, Pooled OR 0.33(95% CI, 0.09 to 1.18)	
Chen, 2007	NR	Risk of myocardial infarction Celecoxib vs Placebo Event/Number: 37/5632 vs 9/2551, OR 1.68 (95% CI 0.82 to 3.42).No evidence of heterogeneity, $I^{2\ =0.00\%}$ p=NS Risk of myocardial infarction with Celecoxib >200mg QD is significantly higher than placebo OR 2.25; 95% CI 1.06 to 4.77 Celecoxib vs any NSAID Event/Number: 51/17678 vs 43/11890, OR 1.51 (95% CI 0.93 to 2.45). No evidence of heterogeneity. Celecoxib vs naproxen: Pooled OR (95% CI) 1.26 (0.41 to 3.90), test for heterogeneity p= 0.99 , I^2=0.00% Celecoxib vs diclofenac: Pooled OR (95% CI)1.28 (0.71 to 2.31),test for heterogeneity p=0.62 , I^2=0.00% Celecoxib vs Ibuprofen: Pooled OR (95% CI) 2.16 (0.83 to 5.61), test for heterogeneity p=0.20 , I^2=39.90%	

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs
Chou, et al 2006	To assess the comparative effectiveness and safety of analgesics in the treatment of OA	1966-2005 (*some additional post-search studies included)	Systematic reviews and RCTs that compared one included drug to another, another active comparator, or placebo; cohort and case-control studies with at least 1,000 cases or participants that evaluated serious GI and cardiovascular endpoints that were inadequately addressed by randomized controlled trials.	Not specified	Systematic reviews, RCTs, observational studies (for safety only) 351 publications, some relating to drugs outside the scope of this report (e.g. acetaminophen, topical analgesics)

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(6) Characteristics of identified articles: populations	(7) Characteristics of identified articles: interventions	(8) Main results
Chou, et al 2006	Patients with OA for efficacy; any indication for safety	Oral analgesics. Agents of interest for this report include: celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate sodium, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate and sulindac	Efficacy: No statistically significant differences in efficacy were found when one non-selective NSAID was compared to another, or when a non-selective NSAID was compared to celecoxib Safety: Non-selective NSAIDs: No particular non-selective NSAID was associated with increased GI risk when compared to another non-selective NSAID; all non-selective NSAIDs appear to equally increase risk of serious GI events compared to non-use. For non-selective, non-naproxen NSAIDs, there was also no difference in CV risk. Based on limited evidence, the risk of CV events appears to be modestly lower for naproxen when compared to other non-selective NSAIDs and celecoxib. CV risk for naproxen was neutral compared to placebo based on indirect analysis. Celecoxib: Systematic reviews and many meta-analyses of short-term, low dose use celecoxib found fewer UGI complications when compared to non-selective NSAIDs. Data is mixed regarding CV risk and celecoxib. Some meta-analyses have found no increased risk associated with celecoxib use compared to non-selective NSAIDs and placebo, while two more recent trials have found celecoxib use to be associated with an increased risk of MI relative to placebo use. Data from observational studies regarding CV risk are also mixed.

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Chou, et al 2006	No evidence suggested a difference in efficacy based on age, gender or racial group For safety, there is an increased risk of GI and CV complications in elderly populations, however no particular non-selective NSAID appeared to be associated with an increased risk. One observational study found higher rate of death when celecoxib was compared to diclofenac and ibuprofen (compared to non-use, one additional death/year of treatment occurred for every 14 celecoxib pts, every 24 diclofenac pts, and every 45 ibuprofen pts)	see Main Results	

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs
Huang, 1999	Evaluate the risk of GI adverse events: rate of perforations, ulcers and bleeds	1980-1998	Comparative RCTs with raw data on perforations, ulcers and bleeds; adult patients with RA, OA or other musculoskeletal disorders; each treatment arm to include>10 patients and publications should be English	Nonendoscopic: 7468 patients Non endoscopic: 244 patients Postmarketing open label studies: 41,789 patients	comparative RCTs; long term post-marketing, open label or extended studies

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(6) Characteristics of identified articles: populations	(7) Characteristics of identified articles: interventions	(8) Main results
Huang, 1999	Patients with RA, OA or other musculoskeletal disorders	Nabumetone and conventional NSAIDS	NR (see adverse events)

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Huang, 1999	NR	Non endoscopic comparative studies Nabumetone vs comparator NSAIDs % of patients experiencing GI events: 25.3% vs 28.2%, p=0.007, a significant difference was seen only at 6 mos, p<0.0001 % of patients with perforations, ulcers and bleeds: 0.062% vs 0.916%, p<0.0001, difference significant at 4 mos (p=0.004) and 6 mos(p=0.0041) % of patients with perforations, ulcers and bleeds per 100 patient-exposure years: 0.087% vs 2.882%, OR 35.5 (95% CI, 5.3 to 757.5) Endoscopic comparative studies % of patients with perforations, ulcers and bleeds: 2.6% vs 21% % of patients with perforations, ulcers and bleeds per 100 patient-exposure years: 2.5 vs 20.9, OR 10.11 (95% CI, 2.8 to 43.5) % Dropouts due to GI related AE : 8.64 vs 11.26, OR 1.3 (95% CI 1.1 to 1.6) % of treatment related hospitalizations per 100-patient exposure yrs: 0.18% vs 2.03%, OR 3.7 (95% CI, 1.3 to 10.7)	

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs
Riedemann, 1993	To assess the effect of tenoxicam vs other NSAIDs	1980-1990	Studies on OA treatment with tenoxicam and either piroxicam, diclofenac or indomethacin	4174 patients: 3196 tenoxicam vs piroxicam; 757 tenoxicam vs diclofenac; 221 tenoxicam vs indomethacin	18 studies- all included studies had some of the following criteria: 1) random allocation 2) double-blinded 3) reported outcomes 4) sufficient numerical data for statistical analysis 5) min. 4 weeks of treatment
Roelofs, 2010	To assess the effects of NSAIDS and Cox-2 inhibitors in the treatment of non-specific low-back pain and to assess which type of NSAID is most effective	1966-June 2007	Randomized trials and double blind controlled trials of NSAIDS in non specific low-back pain with or without sciatica	11,237 patients	Randomized trials (DB, single blind, open label) and DB controlled trials

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(6) Characteristics of identified articles: populations	(7) Characteristics of identified articles: interventions	(8) Main results
Riedemann, 1993	NR	tenoxicam 20-40 mg/day vs. -piroxicam 20 or 40 mg/day (13 studies) or -diclofenac 100 mg/day (4 studies) or -indomethacin 75 mg/day	Efficacy: Tenoxicam vs piroxicam - Patients treated with tenoxicam were 1.46 (OR 1.46) times more likely to receive a "good" or "excellent" efficacy rating for outcome measures (generally Likert scale) than piroxicam patients (CI 1.08-2.03) Tenoxicam vs diclofenac - no SS difference between treatment groups (OR 1.23, 95% CI: 0.89-1.70) Tenoxicam vs indomethacin - no SS difference between treatment groups (rates not reported)
Roelofs, 2010	Adults with non specific low-back pain with or without sciatica. Both acute (12 weeks or less) and chronic (more than 12 weeks) low back-pain patients were included	One or more types of NSAIDs. Additional interventions were allowed if there was a contrast for NSAIDs in the study. For example, studies comparing NSAIDs plus muscle relaxants.	NSAID vs Placebo: Acute low back pain on patients with non-sciatic mixed acute low back pain WMD (weighted mean difference) was -8.39 (95% CI -12.68 to -4.10), statistically significant effect in favor of NSAIDs compared to Placebo, Test for heterogeneity: statistically homogeneous studies; Chi-square 3.47; p>0.1 Acute low back pain for patients with Sciatica only: WMD -0.16, (95% CI , -11.92 to 11.52), no statistical difference in effect between NSAID and Placebo. Test for heterogeneity(Chi-square 7.25; p<0.01) Pooled RR (risk ratio) for global improvement after one week using fixed effects model: 1.19 (95% CI 1.07 to 1.33), studies statistically homogeneous Chronic low back pain WMD -12.40 (95% CI -15.53 to -9.26), Chi-square for homogeneity: p>0.05

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Riedemann, 1993	NR	Specific AEs were not reported for any interventions. There was no SS difference in percentages of patients reporting adverse events for tenoxicam vs. piroxicam or tenoxicam vs diclofenac. For tenoxicam vs indomethacin (2 studies) there was a SS lower rate of AEs for tenoxicam (pooled risk -0.27, p=0.0002). Number of dropouts due to AEs was 17% lower with tenoxicam vs piroxicam. For tenoxicam vs diclofenac and tenoxicam vs indomethacin, so SS difference was reported in dropouts.	One study (tenoxicam 40 mg/day vs piroxicam 40mg/day) was excluded from efficacy analysis for an unspecified reason
Roelofs, 2010	NR	NSAID vs Placebo Acute Low back pain No heterogeneity among studies comparing NSAIDs to placebo, Pooled RR (risk ratio) for side effects 1.35 (95% CI 1.09 to 1.68) Chronic low back pain No heterogeneity among studies, pooled RR for side effects 1.24 (95% CI 1.07 to 1.43)	

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs
Rostom, 2010	To review the effectiveness of common interventions for the prevention of NSAID induced upper GI toxicity	1966-May 2009	RCTs of prostaglandin analogues, H2 receptor antagonists or proton pump inhibitors for the prevention of chronic NSAID induced GI toxicity were included.	Not specified	RCTs
Sorkin EM, Brogden RN 1985	Review of pharmacological properties and therapeutic efficacy in RA, OR and other rheumatic diseases	? - 1985	Not specified, although all published studies of tiaprofenic acid appear to be included	Not specified	Open label and randomized controlled trials - unspecified number of short-term (< 3 mos) studies

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(6) Characteristics of identified articles: populations	(7) Characteristics of identified articles: interventions	(8) Main results
Rostom, 2010	Patients who had taken NSAIDs for greater than 3 weeks and were enrolled for the prophylaxis of NSAID induced ulcers.	H2-antagonists, proton pump inhibitors, and misoprostol each used for the prophylaxis of NSAID induced gastroduodenal ulcers.	NR. See Adverse events
Sorkin EM, Brogden RN 1985	Patients with RA, OA, "other rheumatic diseases"	tiaprofenic acid 600 mg/day vs: aspirin 3600 mg/day diclofenac 150 mg/day ibuprofen 1200 mg/day indomethacin 75-105 mg/day naproxen 500 mg/day piroxicam 20 mg/day sulindac 300 mg/day placebo	Similar effectiveness vs. all comparators except placebo - more effective that placebo Pooled data not provided; absolute values not provided

Evidence Table 5. Data abstraction of systematic reviews

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Rostom, 2010	NR	All doses of misoprostol significantly reduced the risk of endoscopic ulcers. Misoprostol 800ug/day was superior to 400ug/day for the prevention of endoscopic gastric ulcers (RR0.17 and RR0.39 respectively, p=0.0055. Misoprostol caused diarrhea at all doses, significantly more at 800ug/day (p=0.0012) Standard H2RAs were effective at reducing the risk of endoscopic duodenal ulcer (RR 0.36; 95% CI 0.18 to 0.74) but not gastric ulcers (RR0.73; 95% CI 0.50 to 1.08). Both double dose H2RA and Proton pump inhibitor were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74), gastric ulcer RR =0.40; 95% CI 0.32 to 0.51) and were better tolerated than misoprostol	
Sorkin EM, Brogden RN 1985	NR	Statistically significant percentage of patients reported fewer GI side effects with tiaprofenic acid v indomethacin (3.7% v 7.8% nausea and vomiting; 9.5% vs 23.4% dyspepsia or other GI) Similar rates of AEs for other comparators	

Evidence Table 6. Quality assessment of systematic reviews

Author Year	Report clear review question, state inclusion and exclusion criteria of primary studies?	Substantial effort to find relevant research?	Adequate assessment of validity of included studies?	Sufficient detail of individual studies presented?	Primary studies summarized appropriately?
Roelofs 2010	Yes	Yes	Yes	Yes	Yes
Chen 2006	Yes	Yes	Yes	Yes	Yes
Chen 2007	Yes	Yes	Yes	Yes	Yes
Huang 1999	Yes	Yes	No	Yes	Yes
Rostom 2010	Yes	Yes	Yes	Yes	Yes