Therapeutic Class Overview
NSAID Gastroprotective Combination Agents and COX-2 Inhibitor

INTRODUCTION

- Non-steroidal anti-inflammatory drugs (NSAIDs) are useful in the treatment of several different types of pain. NSAIDs exert their effect through the inhibition of cyclooxygenase (COX), which impairs the transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. The two isoforms of the COX enzyme are COX-1 and COX-2. COX-1 is expressed in most tissues and regulates normal cellular processes (ie, gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function). COX-2 is expressed mainly in the brain, kidney, and bone. However, it has increased expression at other sites with inflammation (Meade et al, 1993; De Witt et al, 1993). Differences in the extent of COX-1 and COX-2 inhibition affect the activity and toxicity of individual NSAIDs.
- NSAIDs may cause gastrointestinal (GI) ulceration and bleeding. There is a 4-fold increased risk for GI bleeding or perforation in patients who use NSAIDs (Hernandez-Diaz et al, 2002; Masso et al, 2010).
    - An estimated 25% of chronic NSAID users will develop ulcer disease, and 2 to 4% will develop a GI bleed or perforation. Risk factors for an NSAID-associated GI event include high NSAID dose, advanced age, history of peptic ulcer (especially bleeding ulcer), concomitant use with corticosteroids or anticoagulants, and cardiovascular disease (Lanza et al, 2009).
- NSAIDs have been associated with an increased risk for cardiovascular events such as heart attack and stroke. Some nonselective NSAIDs, including diclofenac and ibuprofen, have demonstrated comparable cardiovascular risk to COX-2 inhibitors. Naproxen is associated with lower cardiovascular risk than other NSAIDs (Bhala et al, 2013).
- All NSAIDs carry boxed warnings for both GI and cardiovascular risks. It is important to evaluate GI and cardiovascular risk factors in patients requiring NSAID therapy (Lanza et al, 2009).
- For patients with a high risk for GI events, a selective COX-2 inhibitor may be preferred over a nonselective NSAID. Gastroprotective agents are also available to reduce the risk of NSAID-associated GI events. These agents include an exogenous prostaglandin (misoprostol), histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs).
- This review encompasses two classes: the NSAID gastroprotective combination agents and the COX-2 inhibitors.
    - NSAID gastroprotective combination agents combine a conventional NSAID with misoprostol, a PPI (esomeprazole), or an H2RA (famotidine). Available products within this class include ARTHROTEC® (diclofenac sodium/misoprostol), VIMOVO® (naproxen/esomeprazole), and DUEXIS® (ibuprofen/famotidine).
    - The only available COX-2 inhibitor is CELEBREX® (celecoxib). Previously available COX-2 inhibitors, VIOXX® (rofecoxib) and BEXTRA® (valdecoxib), were removed from the market in 2004 and 2005, respectively, due to concerns for increased cardiovascular risk (Food and Drug Administration [FDA], 2005).
- ARTHROTEC and CELEBREX are available generically. The other agents discussed in this review are available only as brand-name agents. However, it is important to note that the individual components of the NSAID gastroprotective combination products are all available as single-ingredient products at strengths similar to those included in the combination products (eg, diclofenac sodium, naproxen, esomeprazole, misoprostol, ibuprofen, and famotidine).
- The safety and efficacy of the NSAID gastroprotective combination agents have been established in randomized controlled trials; however, no head-to-head trials exist within this class. The safety and efficacy of celecoxib have been established in randomized controlled trials which compare celecoxib to placebo, conventional NSAIDs, and NSAID gastroprotective combination agents.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ARTHROTEC (diclofenac sodium/misoprostol)	GD SEARLE LLC	12/24/1997	✔
CELEBREX (celecoxib)	GD SEARLE LLC	12/31/1998	✔
DUEXIS (ibuprofen/famotidine)	HORIZON PHARMA	04/23/2011	-
VIMOVO (naproxen/esomeprazole)	HORIZON PHARMA	04/30/2010	*

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*Although generic naproxen/esomeprazole has been approved by the FDA, launch is not anticipated until 2023 based on current patent status.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ARTHROTEC (diclofenac sodium/ misoprostol)	CELEBREX (celecoxib)	DUEXIS (ibuprofen/ famotidine)	VIMOVO (naproxen/ esomeprazole)
Management of acute pain in adults		✔		
Management of primary dysmenorrhea		✔		
Management of the signs and symptoms of ankylosing spondylitis		✔		
Management of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older		✔		
Management of the signs and symptoms of osteoarthritis		✔		
Management of the signs and symptoms of rheumatoid arthritis		✔		
Relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers				✔
Relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper GI ulcers, which in the clinical trials was defined as a gastric and/or duodenal ulcer, in patients who are taking ibuprofen for those indications			✔	
Treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications	✔			

(Prescribing information: ARTHROTEC, 2016; CELEBREX, 2016; DUEXIS, 2016; VIMOVO, 2016)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

NSAID/Gastroprotective Combination Agents

- A Cochrane meta-analysis reviewed the effectiveness of misoprostol, H2RAs, and PPIs in the prevention of NSAID-induced upper GI toxicity. The primary outcomes of endoscopic gastric ulcers (GUs) and duodenal ulcers (DUs) were evaluated in 44 randomized controlled trials with patients on traditional NSAIDs for arthritis (23 misoprostol, 12 H2RA, and 9 PPI trials). Misoprostol, double doses of H2RAs, and PPIs all demonstrated a benefit over placebo in reducing the risk for NSAID-associated GUs (relative risk [RR]=0.26, 0.44, and 0.39, respectively) and DUs (RR=0.42, 0.26, and 0.20, respectively). Standard dose H2RAs reduced the risk for DUs (RR=0.24) but not GUs (Rostom et al, 2002).
- A randomized controlled trial demonstrated that ARTHROTEC has comparable efficacy to diclofenac monotherapy for the treatment of osteoarthritis (OA) and is associated with a lower rate of GUs and DUs (Bocanegra et al, 1998). Additionally, the combination agent has demonstrated comparable efficacy to that of naproxen and piroxicam

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monotherapy for the treatment of OA and is associated with a lower rate of gastric and duodenal ulcers compared to naproxen, piroxicam, and nabumetone monotherapy (Agrawal et al, 1999; Melo Gomes et al, 1993). In comparison to acetaminophen (APAP) monotherapy for the treatment of OA, diclofenac sodium/misoprostol is superior in terms of efficacy but is associated with higher GI distress and incidence of adverse events (AEs) (Pincus et al, 2001).

- The safety and efficacy of DUEXIS were evaluated in the REDUCE-1 (N=906) and REDUCE-2 (N=627) trials. Both double-blind, randomized controlled trials were 24 weeks in duration and compared ibuprofen 800 mg/famotidine 26.6 mg three times daily to ibuprofen 800 mg alone three times daily. In the pooled analysis, the incidence of GUs was 12.5% in the combination group and 20.7% in the ibuprofen group; the incidence of DUs was 1.1 and 5.1%, respectively. The risk ratio of upper GI ulcers for ibuprofen/famotidine vs ibuprofen alone was 0.46 (95% confidence interval [CI], 0.34 to 0.61). Although endoscopically-confirmed ulcers were reduced, there was no demonstrated benefit in GI complications (Laine et al, 2012). Another pooled analysis showed that DUEXIS maintained the same gastroprotective efficacy and contributed to a 51% and 59% risk reduction for GI ulcer development in patients aged < 60 years old and ≥ 60 years old, respectively, when compared to treatment with ibuprofen alone. The combination also remained effective for patients with additional risk factors for GI ulcer development (Bello et al, 2015).
- The efficacy and tolerability of VIMOVO for OA, RA, and ankylosing spondylitis were evaluated in a systematic review and network meta-analysis of 109 randomized controlled trials comparing VIMOVO, naproxen, diclofenac, ibuprofen, ketoprofen, celecoxib, or etoricoxib (Datto et al, 2013).
    - VIMOVO demonstrated comparable efficacy to all active comparators in the relief of symptoms of OA, RA, and ankylosing spondylitis.
    - Through direct meta-analysis, VIMOVO was associated with a lower risk of GU than naproxen monotherapy (odds ratio [OR]=0.17; 95% CI, 0.10 to 0.31). There was no significant difference in the incidence of GUs in direct comparisons between VIMOVO and celecoxib.
    - Through indirect mixed treatment comparison, VIMOVO-treated patients had significantly lower odds of GU occurrence compared with ibuprofen (OR=0.25; 95% credible interval [CrI], 0.10 to 0.56) and diclofenac (OR=0.43; 95% CrI, 0.18 to 0.90). No significant differences were detected in the incidence of GU between VIMOVO and ketoprofen, etoricoxib, celecoxib, or fixed-dose diclofenac sodium plus misoprostol.
- Another systematic review of 5 Phase 3 studies for VIMOVO was conducted to analyze the incidence of ulcers (gastric and duodenal), erosive gastritis, and erosive duodenitis in patients receiving concomitant low-dose aspirin (LDA) therapy (Angiolillo et al, 2014).
    - In the 2 trials with 6-month follow-up, the combined incidence of GUs was lower for the VIMOVO vs EC naproxen groups regardless of LDA use (P<0.001 for both LDA users and non-users).
    - The combined incidence of erosive gastritis from the 2 trials was also lower in VIMOVO vs EC naproxen-treated patients for both LDA users (P=0.004) and LDA non-users (P<0.001).

Celecoxib

- Celecoxib has been compared to conventional NSAIDs in several clinical trials for the treatment of OA. In general, selective COX-2 inhibitors have comparable efficacy to conventional NSAIDs such as piroxicam, naproxen, diclofenac, ibuprofen, and nabumetone. There is a difference in the reported tolerability of NSAIDs; specifically, celecoxib is associated with less GI AEs than conventional NSAIDs (Bensen et al, 1999; Chan et al, 2002; Silverstein et al, 2000; Singh et al, 2006). However, one 12-week, double-blind, parallel-group, randomized trial (N=249) failed to demonstrate noninferiority of celecoxib 200 mg daily to diclofenac 50 mg three times daily in patients with OA of the hip requiring joint replacement surgery (Emery et al, 2008).
- In the 12-week, randomized, multicenter, double-blinded SUCCESS-I study (N=13,274), the comparative efficacy and safety of celecoxib, diclofenac, and naproxen were evaluated. Celecoxib demonstrated comparable efficacy to diclofenac and naproxen in the treatment of OA. Nonselective NSAIDs were associated with significantly more ulcer complications than celecoxib (OR=7.02; 95% CI, 1.46 to 33.80; P=0.008) (Singh et al, 2006).
- Several trials have compared celecoxib with conventional NSAIDs for the relief of symptoms associated with rheumatoid arthritis (RA). Results of two studies comparing celecoxib with diclofenac and naproxen demonstrated similar efficacy (Emery et al, 1999; Simon et al, 1999). In addition, a study was conducted to compare the efficacy of celecoxib to naproxen among children with juvenile rheumatoid arthritis (JRA). Study results revealed that celecoxib was at least as effective as naproxen in treating the symptoms of JRA over 12 weeks (Foeldvari et al, 2009).
- A double-blind study compared celecoxib 200 mg twice a day to a combination of diclofenac slow-release 75 mg twice a day and omeprazole 20 mg daily in patients with either OA or RA at increased risk for GI AEs. The primary endpoint of clinically significant upper or lower GI events occurred in 0.9% of patients taking celecoxib and 3.8% of patients receiving diclofenac plus omeprazole (P<0.0001) (Chan et al, 2010).

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- Several clinical trials were conducted to evaluate the use of celecoxib for the management of pain. In general, comparable analgesic effects were noted between celecoxib and other NSAIDs (ie, ibuprofen, naproxen) (Derry et al, 2012; Loo et al, 2007; Salo et al, 2003). Some trials demonstrated differences between celecoxib and ibuprofen for pain relief following minor oral surgery procedures; however, data has been inconsistent and may be dose-dependent (Doyle et al, 2002; Al-Sukhun et al, 2012).
    - One clinical trial compared the efficacy of varying doses of celecoxib to indomethacin for the treatment of acute gout. The higher dose regimen of celecoxib (800 mg for one dose, followed by 400 mg twice daily through a total of eight days of therapy) was demonstrated to have equal efficacy to indomethacin 50 mg three times daily, with improved tolerability (Schumacher et al, 2012). Although indicated for the treatment of acute pain, celecoxib is not specifically indicated for the treatment of gout, and the dose regimen in this study is higher than recommended in the celecoxib prescribing information.
- The efficacy of celecoxib for the treatment of primary dysmenorrhea was evaluated in 2 identical randomized, double-blind, active and placebo-controlled, crossover trials. Celecoxib and naproxen demonstrated a benefit over placebo in the primary outcome of time-weighted sum of total pain relief (P<0.001 for both) and the secondary outcome of time-weighted sum of pain intensity difference at 8 hours after administration (SPID[8]) (P<0.001 for both). However, naproxen established a greater improvement in SPID[8] than celecoxib (P<0.001) (Daniels et al, 2009).

Guidelines

- For moderate acute pain, NSAIDs are more effective than acetaminophen (APAP) and aspirin. Some NSAIDs have demonstrated efficacy for moderate acute pain that is equal to or greater than that of APAP/opioid combination products. Celecoxib has similar efficacy to non-selective NSAIDs for the treatment of OA and RA. Comparative efficacy among NSAIDs is not well established (Medical Letter, 2013).
- NSAIDs play an important role in the treatment of several conditions, including RA, OA, ankylosing spondylitis, juvenile idiopathic arthritis, low back pain, dysmenorrhea, and gout. Cardiovascular, GI, and renal risks should be taken into account when prescribing an NSAID (Beukelman et al, 2011; Braun et al, 2011; Chou et al, 2007; Hochberg et al, 2012; Khanna et al, 2012; Lanza et al, 2009; Medical Letter, 2013; Society of Obstetricians and Gynecologists of Canada, 2005).
- According to the American College of Gastroenterology (ACG), the selection of an appropriate NSAID therapy should consider cardiovascular and GI risk factors in addition to analgesic and anti-inflammatory potency (Lanza et al, 2009).
    - Patients at high risk for GI complications (eg, prior ulcer bleeding or multiple risk factors) are recommended alternative therapy to NSAIDs. If anti-inflammatory therapy is required, a selective COX-2 inhibitor in combination with misoprostol or a high-dose PPI should be used.
    - Patients at moderate risk for GI complications are recommended NSAID therapy with a COX-2 inhibitor or a nonselective NSAID in combination with misoprostol or a PPI.
    - Patients at low risk for GI complications are candidates for therapy with a nonselective NSAID.
    - Patients who require low-dose aspirin therapy for cardiovascular disease and NSAID therapy should receive naproxen in combination with misoprostol or a PPI.
    - Patients with a moderate risk for GI complications and high cardiovascular risk should be treated with naproxen in combination with misoprostol or a PPI.
    - Patients with high GI and high cardiovascular risk should avoid using NSAIDs, including COX-2 inhibitors.
- The American College of Rheumatology, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network recommend NSAID therapy in adults with active ankylosing spondylitis. For patients with stable ankylosing spondylitis, on demand treatment with NSAIDs is preferred over continuous treatment (Ward et al, 2016).
- In 2015, the International NSAID Consensus Group released recommendations for NSAID use in patients with OA (Scarpignato et al, 2015).
    - COX-2 inhibitors and non-selective NSAIDs have the same efficacy for pain management in patients with RA or OA.
    - NSAID-related AEs are not prevented by PPIs in the lower GI areas (beyond the duodenum). Celecoxib causes less AEs than nonselective NSAIDs throughout the entire GI system.
    - The risk for cardiovascular events is similar between celecoxib and most non-selective NSAIDs. The literature shows that naproxen causes the least amount of cardiovascular AEs among non-selective NSAIDs.

SAFETY SUMMARY

- Key contraindications to all NSAID-containing products include:

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  - Treatment of peri-operative pain in the setting of coronary artery bypass graft surgery
  - History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs
- Celecoxib is contraindicated in patients with a history of allergic-type reactions to sulfonamides.
- ARTHROTEC is contraindicated in patients with active GI bleeding.
- ARTHROTEC is also contraindicated throughout pregnancy; DUEXIS, VIMOVO, and celecoxib should be avoided in late pregnancy because NSAIDs can cause premature closure of the ductus arteriosus in the fetus.
- All NSAIDs, including celecoxib, have boxed warnings for the risk of serious and potentially fatal cardiovascular and GI events.
  - Serious cardiovascular thrombotic reactions (ie, myocardial infarction and stroke) may occur as early as the first weeks of treatment. The risk may increase with higher dosage and longer duration of use. NSAIDs are contraindicated in the setting of coronary artery bypass graft (CABG) surgery.
  - Serious GI adverse reactions (ie, bleeding, ulceration, and perforation of the stomach or intestines) may occur without warning symptoms at any time during therapy. The risk is higher for elderly patients and patients with a history of PUD or GI bleeding.
- ARTHROTEC labeling also includes a boxed warning for the risk of uterine rupture, abortion, premature birth, and birth defects in pregnant women caused by misoprostol.
- Additional key warnings and precautions for NSAIDs include:
  - New onset or worsening of hypertension
  - Congestive heart failure and edema
  - Renal injury and renal papillary necrosis with long-term use
  - Serious skin reactions
  - Elevated liver enzymes, hepatotoxicity, and rare severe hepatic reactions
  - Anemia
  - Inhibition of platelet aggregation
- Key warnings with prolonged use of PPI's (VIMOVO) include:
  - Increased risk of osteoporosis-related fractures
  - Acute interstitial nephritis
  - Potential for anemia, hypomagnesemia, and hypocalcemia
  - Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE)
- The most commonly reported adverse drug events, reported in at least 5% of patients in clinical trials, include:
  - ARTHROTEC: abdominal pain, diarrhea, dyspepsia, nausea, and flatulence
  - Celecoxib: abdominal pain, diarrhea, dyspepsia, nausea, cough, fever, headache, hypertension, nasopharyngitis, and upper respiratory tract infection
  - DUEXIS: nausea, diarrhea, and dyspepsia
  - VIMOVO: erosive gastritis, gastritis, dyspepsia, upper abdominal pain, diarrhea, gastric ulcer, nausea, and upper respiratory tract infection
- Key drug interactions with NSAIDs include:
  - The effects of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, furosemide, and thiazide diuretics may be diminished by concurrent NSAID therapy.
  - Plasma lithium levels may be increased by NSAIDs.
  - Patients on warfarin or other anticoagulants are at an increased risk of bleeding complications.
- The 2015 American Geriatrics Society (AGS) Beers Criteria recommends avoiding chronic use of non-selective NSAIDs in older adults. NSAIDs increase the risk of GI bleeding and peptic ulcer disease in high-risk groups (ie, age >75, concomitant use of anticoagulants or systemic corticosteroids). While the addition of gastroprotective agents reduces GI risk, it does not eliminate it (AGS, 2015).
- The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial evaluated the cardiovascular safety of celecoxib 200 mg twice daily compared with ibuprofen 800 mg three times daily and naproxen 500 mg twice daily. The randomized, multicenter, double-blind, noninferiority trial included 24,081 patients with increased cardiovascular risk who required NSAID therapy for OA or RA. The primary outcome measure was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcome measures included GI and renal safety (Nissen et al, 2016).
  - Celecoxib was noninferior to ibuprofen and naproxen with regards to cardiovascular safety. In the intent-to-treat population, a primary outcome event occurred in 2.3% of the celecoxib group, 2.5% of the naproxen group, and 2.7% of the ibuprofen group (hazard ratio [HR]=0.93 vs naproxen, HR=0.85 vs ibuprofen; P<0.001 for noninferiority to both).

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- Celecoxib was associated with a lower incidence of GI adverse events compared to naproxen (P=0.01) and ibuprofen (P=0.002).
- Celecoxib was also associated with a significantly lower incidence of renal adverse events compared with ibuprofen (P=0.004). Statistical significance was not reached when compared with naproxen (P=0.19).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
ARTHROTEC (diclofenac sodium/ misoprostol)	Film-coated tablet: 50 mg/200 mcg 75 mg/200 mcg	OA 50 mg/200 mcg three times daily; alternative regimens due to intolerance*: 75 mg/200 mcg tablet twice daily or 50 mg/200 mcg twice daily RA 50 mg/200 mcg three or four times daily; alternative regimens due to intolerance*: 75 mg/200 mcg or 50 mg/200 mcg twice daily	Dosages may be individualized using the separate products (misoprostol and diclofenac), after which the patient may be changed to the appropriate dose of ARTHROTEC. If clinically indicated, the concomitant use of misoprostol and ARTHROTEC, or the use of individual components, may be appropriate to optimize the misoprostol dose and/or frequency of administration.
CELEBREX (celecoxib)	Capsule: 50 mg 100 mg 200 mg 400 mg	OA 200 mg once daily or 100 mg twice daily RA 100 to 200 mg twice daily JRA (Pediatric patients ≥ 2 years) Patients ≥10 kg to ≤25 kg: 50 mg twice daily Patients >25 kg: 100 mg twice daily Ankylosing spondylitis 200 mg once daily in a single dose or 100 mg twice daily; if no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit Acute pain and primary dysmenorrhea 400 mg initially, followed by 200 mg dose if needed on first day; on subsequent days, 200 mg twice daily as needed	For patients who have difficulty swallowing capsules, the contents of a CELEBREX capsule can be added to applesauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions (2 to 8° C; 35 to 45° F).
DUEXIS (ibuprofen/ famotidine)	Film-coated tablets: 800 mg/26.6 mg	RA and OA 800 mg/26.6 mg administered orally three times per day	DUEXIS tablets should be swallowed whole. Do not chew, divide, or crush tablets.
VIMOVO (naproxen/ esomeprazole)	Delayed-release tablet: 375 mg/20 mg 500 mg/20 mg	OA, RA, and ankylosing spondylitis 375 mg/20 mg or 500 mg/20 mg twice daily	Tablets should be swallowed whole (not split, crushed, chewed, or dissolved) with liquid and taken at least 30 minutes before meals. Use

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Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
			the lowest effective dose for the shortest duration consistent with individual patient treatment goals

*Less effective in preventing ulcers.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ARTHROTEC (diclofenac sodium/ misoprostol)	No dosage adjustment required in the elderly.	The effectiveness and safety in pediatric patients have not been established	Not recommended in advanced renal disease unless benefits are expected to outweigh the risks	Drug-induced liver injury has been reported with diclofenac; use the lowest effective dose for the shortest possible duration	Pregnancy category X Excreted in breast milk; use with caution
CELEBREX (celecoxib)	Dose adjustment is usually not necessary in elderly patients. Elderly patients < 50 kg: initiate therapy at the lowest recommended dosage	Safety and efficacy have been established in children 2 years of age or older and for a maximum of 6 months of treatment in JRA.	Not recommended in patients with severe renal insufficiency If treatment with celecoxib is necessary, monitor patients renal function closely	The daily dose of celecoxib should be reduced by 50% in patients with moderate hepatic impairment. Celecoxib is not recommended for patients with severe hepatic impairment.	Pregnancy category C Pregnancy category D (starting at 30 weeks gestation) Limited data shows low levels in breast milk; use with caution
DUEXIS (ibuprofen/ famotidine)	No dosage adjustment required; initiate dose at the lower end of the dosing range and monitor for adverse reactions	The effectiveness and safety in pediatric patients have not been established	Not recommended in patients with creatinine clearance <50 mL/min	The effects of hepatic dysfunction have not been evaluated.	Avoid use in pregnant women starting at 30 weeks of gestation (3rd trimester) Excreted in breast milk; use with caution
VIMOVO (naproxen/ esomeprazole)	Use caution when high doses are required and some adjustment of dosage may be required in elderly patients	The effectiveness and safety in pediatric patients have not been established	Not recommended for use in moderate to severe or severe renal insufficiency	Not recommended for use in patients with severe hepatic impairment Dosage adjustment should be considered in mild or moderate hepatic impairment	Avoid use in pregnant women starting at 30 weeks of gestation Limited data shows levels in

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Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
					breast milk; use with caution

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category D = Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may justify the use of the drug in pregnant women despite potential risks.
Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

(Clinical Pharmacology, 2017)

CONCLUSION

- NSAIDs are useful in the treatment of several different types of pain; however, potential GI and cardiovascular adverse events must be considered when selecting an NSAID for drug therapy (Lanza et al, 2009).
- Due to COX-1 inhibition, NSAIDs are associated with GI adverse reactions, including dyspepsia, bleeding, and peptic ulcer disease. To decrease GI risk, clinicians may select a COX-2 selective NSAID (celecoxib) or add a gastroprotective agent to NSAID therapy. The gastroprotective agent may be given separately or as a fixed-dose combination product. ARTHROTEC (diclofenac sodium/misoprostol), VIMOVO (naproxen/esomeprazole), and DUEXIS (ibuprofen/famotidine) are the currently available NSAID gastroprotective combination agents.
- Clinical trials have demonstrated that the combination NSAID gastroprotective combination agents produce comparable anti-inflammatory effects to NSAIDs alone and are associated with a lower incidence of gastric and duodenal ulcers. The individual components of the NSAID gastroprotective combination products are all available as single-ingredient products at strengths similar to those included in the combination products.
- Placebo and active-controlled trials with celecoxib have demonstrated comparable efficacy to nonselective NSAIDs for its approved indications. The PRECISION trial established the noninferiority of celecoxib with regards to cardiovascular safety compared to ibuprofen and naproxen. Additionally, it confirmed a lower incidence of GI adverse events with celecoxib than with both nonselective NSAID comparators (Nissen et al, 2016).
- Considerations for the selection of an NSAID include analgesic and anti-inflammatory potency as well as GI and cardiovascular risk. In general, patients with moderate GI risk may receive therapy with a COX-2 inhibitor or a conventional NSAID plus a gastroprotective agent. Patients requiring NSAID therapy with high GI risk should receive alternative therapy. If anti-inflammatory treatment necessary, a COX-2 inhibitor may be used in combination with misoprostol or a high-dose PPI. Patients at high GI and high cardiovascular risk should avoid using NSAIDs and COX-2 inhibitors (Lanza et al, 2009).

REFERENCES

- Agrawal NM, Caldwell J, Kivitz AJ, et al. Comparison of the upper gastrointestinal safety of Arthrotec 75 and nabumetone in osteoarthritis patients at high risk for developing nonsteroidal anti-inflammatory drug-induced gastrointestinal ulcers. Clin Ther. 1999 Apr;21(4):659-74.
- Al-Sukhun J, Al,-Sukhun S, Pentilla H, et al. Preemptive analgesic effect of low doses of celecoxib is superior to low doses of traditional nonsteroidal anti-inflammatory drugs. J Craniofac Surg. 2012 Mar;23(2):526-9.
- American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2015;63(11)2227-2246. doi: 10.1111/jgs.13702.
- Angiolillo DJ, Datto C, Raines S, et al. Impact of concomitant low-dose aspirin on the safety and tolerability of naproxen and esomeprazole magnesium delayed-release tablets in patients requiring chronic nonsteroidal anti-inflammatory drug therapy: an analysis from 5 Phase III studies. J Thromb Thrombolysis. 2014 Jul;38(1):11-23. doi: 10.1007/s11239-013-1035-4.
- ARTHROTEC prescribing information. Pfizer – GD Searle, New York, NY. May 2016.
- Bello AE, Kent JD, Holt RJ. Gastroprotective efficacy and safety of single-tablet ibuprofen/famotidine vs ibuprofen in older persons. Phys Sportsmed. 2015; 43(3):193-199.
- Bensen WG, Fiechtner JJ, McMillen JI, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. Mayo Clin Proc. 1999;74:1095-105.
- Beukelman T, Nivedita M, Saag K, et al. American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res. 2011 Apr;63(4):465-82. doi: 10.1002/acr.20460.

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- Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013 Aug 31;382(9894):769-79. doi: 10.1016/S0140-6736(13)60900-9.
- Bocanegra TS, Weaver AL, Tindall EA, et al. Diclofenac/ misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo controlled trial. Arthrotec Osteoarthritis Study Group. J Rheumatol. 1998;25(8):1602-11.
- Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011 Jun;70(6):896-904. doi: 10.1136/ard.2011.151027.
- CELEBREX prescribing information. Pfizer. New York, NY. May 2016.
- Chan FK, Hung LC, Suen BY, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. N Engl J Med. 2002;347:2104-10.
- Chan FK, Lanas A, Scheiman J, et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomized trial. Lancet. 2010 Jul 17;376(9736):173-9.
- Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Int Med. 2007 Oct 2;147(7):478-91.
- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: http://www.clinicalpharmacology-ip.com/default.aspx. Accessed March 2, 2017.
- Daniels S, Robbins J, West CR, et al. Celecoxib in the treatment of primary dysmenorrhea: results from two randomized, double-blind, active- and placebo-controlled, crossover studies. Clin Ther. 2009 Jun;31(6):1192-208.
- Datto C, Hellmund R, Siddiqui MK. Efficacy and tolerability of naproxen/esomeprazole magnesium tablets compared with non-specific NSAIDs and COX-2 inhibitors: a systematic review and network analyses. Open Access Rheumatol. 2013 Feb 26;5:1-19. doi:10.2147/OARRR.S41420.
- De Witt DL, Meade EA, Smith WL. PGH synthase isoenzyme selectivity: The potential for safer nonsteroidal anti-inflammatory drugs. Am J Med. 1993;95:40S.
- Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev. 2012, Issue 3. Art. No.: CD004233. doi: 10.1002/14651858.CD004233.pub3.
- Doyle G, Jayawardena S, Ashraf E, et al. Efficacy and tolerability of nonprescription ibuprofen versus celecoxib for dental pain. Journal of Clinical Pharmacology. 2002;49:912-19.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2015. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 2, 2017.
- DUEXIS prescribing information. Horizon Pharma USA, Inc. Northbrook, IL. May 2016.
- Emery P, Koncz T, Pan S, et al. Analgesic effectiveness of celecoxib and diclofenac in patients with osteoarthritis of the hip requiring joint replacement surgery: a 12-week, multicenter, randomized, double-blind, parallel-group, double-dummy, noninferiority study. Clin Ther. 2008 Jan;30(1):70-83.
- Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomized double-blind comparison. Lancet. 1999;354:2,106-11.
- Foeldvari I, Szer IS, Zemel LS, et al. A prospective study comparing celecoxib with naproxen in children with juvenile rheumatoid arthritis. J Rheumatol. 2009 Jan;36(1):174-82.
- Food and Drug Administration. COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). November 27, 2012. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm429364.htm.. Accessed March 2, 2017.
- Hernandez-Diaz S, Rodriguez LA. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. J Clin Epidemiol 2002;55:157-63.
- Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):465-74.
- Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012;64:1447-61. doi: 10.1002/acr.21773.
- Laine L, Kivitz AJ, Bello AE, et al, on behalf of the REDUCE-1 and REDUCE-2 Study Investigators. Double-blind randomized trials of single-tablet ibuprofen/high-dose famotidine vs ibuprofen alone for reduction of gastric and duodenal ulcers. Am J Gastroenterol. 2012; 107:379-386; doi:10.1038/ajg.2011.443.
- Lanza FL, Chan FKL, Quiqley EMM. Guidelines for the prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728-38.
- Loo CY, Tan HJ, Teh HS, et al. Randomized, open label, controlled trial of celecoxib in the treatment of acute migraine. Singapore Medical Journal. 2007;48(9):834-9.
- Masso Gonzalez EL, Patrignani P, Tacconelli S, et al. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. Arthritis Rheum 2010;62:1592-601.
- Meade EA, Smith WL, De Witt DL. Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal anti-inflammatory drugs. J Biol Chem. 1993;268:6610.
- Medical Letter, Inc. Treatment guidelines from the Medical Letter: Drugs for Pain. 2013;11(128):31-42.
- Melo Gomes JA, Roth SH, Zeeh J, et al. Double-blind comparison of efficacy and gastroduodenal safety of diclofenac/misoprostol, piroxicam, and naproxen in the treatment of osteoarthritis. Ann Rheum Dis. 1993 Dec;52(12):881-5.
- Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med. 2016 Dec 29;375(26):2519-29. doi: 10.1056/NEJMoa1611593.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2015. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 2, 2017.
- Pincus T, Koch GG, Sokka T, et al. A randomized, double-blind, crossover clinical trial of diclofenac plus misoprostol versus acetaminophen in patients with osteoarthritis of the hip or knee. Arthritis Rheum. 2001 Jul;44(7):1587-98.
- Rostom A, Dube C, Wells G, et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database Syst Rev. 2002;(4):CD002296. doi: 10.1002/14651858.CD002296.

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- Salo DF, Lavery R, Varma V, et al. A randomized clinical trial comparing oral celecoxib 200 mg, celecoxib 400 mg, and ibuprofen 600 mg for acute pain. Acad Emerg Med. 2003;10(1):22-30.
- Scarpignato C, Lanas A, Blandizzi C, et al for the International NSAID Consensus Group. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis – an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. BMC Medicine. 2015; 13(55):1-22.
- Schumacher HR, Berger MF, Li-Yu J, et al. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. J Rheumatol. 2012 Sep;39(9):1859-66. doi: 10.3899/jrheum.110916.Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis, the CLASS study. JAMA. 2000;284(10):1247-55.
- Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. JAMA. 1999;282(20):1,921-8.
- Singh G, Fort JG, Goldstein JL, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I study. American Journal of Medicine. 2006;119:255-66.
- Society of Obstetricians and Gynecologists of Canada: Primary dysmenorrhea consensus guideline. J Obstet Gynaecol Can. 2005 Dec;27(12):1117-46.
- VIMOVO prescribing information. Horizon Pharma USA. Deerfield, IL. October 2016.
- Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol. 2016;68(2):282-98.

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