Therapeutic Class Overview
Nonsteroidal Anti-inflammatory Drug/Anti-ulcer Agent Combinations

Overview/Summary:
Collectively, the NSAID/anti-ulcer agent combination products are Food and Drug Administration (FDA)-approved for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis and/or ankylosing spondylitis while also helping to prevent NSAID-induced gastric or duodenal ulcers.[1-3] NSAIDs inhibit the cyclooxygenase (COX) family of enzymes, preventing the conversion of arachidonic acid to prostaglandin G_2 which is the first step of prostaglandin and thromboxane synthesis. Specifically, the inhibition of the COX-2 isoenzyme appears to be associated with the anti-inflammatory properties of NSAIDs.[4] The NSAID-related gastrointestinal adverse reactions can be severe in some patients and can occur at any time during therapy without warning.[5] All NSAID-containing agents are associated with a Black Box Warning regarding the increased risk of serious gastrointestinal adverse reactions including bleeding, ulceration and perforation of the stomach and intestines, which can be fatal.[5] In an attempt to reduce the occurrence of these ulcers, anti-ulcer agent have been given concomitantly with NSAIDs. Each combination's anti-ulcer component is has a distinct mechanism that works to prevent the NSAID-induced ulcers.

The safety and efficacy of these agents in the prevention of NSAID-induced gastric and/or duodenal ulcers is well documented in several clinical trials.[6-16] Current clinical guidelines published by the American College of Gastroenterology to prevent NSAID-induced ulcers stratify treatment strategy based on cardiovascular and gastrointestinal risk but generally recommend misoprostol or a PPI.[17] For the treatment of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, NSAIDs or selective COX-2 inhibitors along with other analgesics such as acetaminophen are considered first line.[18-23] Specific agents include Arthrotec® (diclofenac sodium/misoprostol), Duexis® (ibuprofen/famotidine), and Vimovo® (naproxen/esomeprazole magnesium). All combination products have the same drug-interactions, warnings, precautions and black box warning associated with NSAIDs. Differences between products are based on the other agent in the combination and the dosing. Diclofenac sodium/misoprostol is dosed three to four times a day based on indication while ibuprofen/famotidine is dosed three times a day and naproxen/esomeprazole magnesium is dosed only twice daily.[1-3]

Table 1. Current Medications Available in Therapeutic Class[1-47]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Diclofenac sodium/ misoprostol (Arthrotec®*)	For the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis and to decrease the risk of developing NSAID-associated duodenal and gastric ulcers	Tablet, DR: 50/0.2 mg 75/0.2 mg	✔
Ibuprofen/ famotidine (Duexis®)	For the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis and to decrease the risk of developing NSAID-associated duodenal and gastric ulcers	Tablet, 800/26.6 mg	-
Naproxen/ esomeprazole magnesium (Vimovo®)	For the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and to decrease the risk of developing NSAID-associated gastric ulcers	Tablet, DR: 375/20 mg 500/20 mg	-

DR=delayed-release
*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Diclofenac sodium/misoprostol (Arthrotec®) has comparable efficacy to diclofenac monotherapy for the treatment of osteoarthritis and is associated with a lower rate of gastric and duodenal ulcers.[6]
    - The combination agent has demonstrated comparable efficacy to that of naproxen and piroxicam monotherapy, and is also associated with a lower rate of gastric and duodenal ulcers compared to naproxen, piroxicam, and nabumetone monotherapy.[7,8]
    - In comparison to acetaminophen monotherapy in terms of efficacy, diclofenac sodium/misoprostol provided statistically significant improvement, but is associated with higher gastrointestinal distress and incidence of adverse events.[9]
- Ibuprofen/famotidine (Duexis®) was evaluated in two phase III clinical trials, REDUCE-1 and REDUCE-2, which included over 1,500 patients diagnosed with mild to moderate pain or arthritis
    - The primary endpoints for REDUCE-1 and REDUCE-2 were the reduction in gastric ulcers during the 24-week treatment period and the reduction in incidence of upper gastrointestinal ulcers during the 24-week period, respectively.[12]
    - Pooled results from both trials indicated that treatment with ibuprofen/famotidine resulted in an absolute risk reduction of 9.6% compared to ibuprofen for the risk of upper gastrointestinal ulcers (95% confidence interval [CI], 5.4 to 13.8).[12]
- Naproxen/esomeprazole magnesium (Vimovo®) was studied two phase III clinical trials (PN400-301 and 302) that evaluated the effectiveness in preventing the occurrence of NSAID-induced gastric ulcers. and two phase III trials that evaluated its effectiveness in the treatment of osteoarthritis (PN400-307 and 309).[1,13,15]
    - Naproxen/esomeprazole magnesium 500 mg/20 mg twice daily significantly reduced the 6-month cumulative incidence of gastric ulcers compared to enteric-coated naproxen 500 mg twice daily ($P<0.001$ for both studies). This translated to a relative risk reduction (RRR) of 82.3% and 70.8% in studies 301 and 302, respectively.[1,13]
    - Naproxen/esomeprazole magnesium arm significantly improved baseline scores of the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subscale and the WOMAC physical function subscale when compared to placebo ($P<0.05$).[1,15]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Current clinical guidelines published by the American College of Gastroenterology to prevent NSAID-induced ulcers stratify treatment strategy based on cardiovascular and gastrointestinal risk.[17]
        - It is recommended that patients receive an NSAID plus either misoprostol or a PPI if they have low or moderate gastrointestinal risk.
        - If the patient has high cardiovascular risk, naproxen is recommended as the NSAID.
        - For patients with high gastrointestinal risk and low cardiovascular risk, a selective COX-2 inhibitor plus a PPI or misoprostol is recommended.
        - Patients with both high gastrointestinal and cardiovascular risk should not receive any type of NSAID therapy.
        - H2-receptor antagonists are much less effective compared to misoprostol or a PPI in preventing ulcers.
    - Generally, NSAIDs or selective COX-2 inhibitors along with other analgesics such as acetaminophen are considered first line for the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.[18-23]
- Other Key Facts:
    - The NSAID is used to treat pain and inflammation while the anti-ulcer agent is used to prevent a common, yet severe adverse event associated with NSAIDs.
    - Each combination's anti-ulcer component has a distinct mechanism of action.[1-3]
    - All agents in this class are tablets and share the same drug-interactions, warnings, precautions and black box warning associated with NSAIDs but differ based on their anti-ulcer component, particularly dosing.

- Diclofenac sodium/misoprostol is dosed three to four times a day based on indication; ibuprofen/famotidine is dosed three times; naproxen/esomeprazole magnesium is dosed twice daily.[1-3]
- Naproxen/esomeprazole magnesium is approved to prevent gastric ulcers and is not indicated to prevent NSAID-associated duodenal ulcers.[3]
- Only diclofenac sodium/misoprostol is available generically as a single-tablet combination.
- As single entity agents, all products are available generically, many of which are available over-the-counter.

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Therapeutic Class Review
Nonsteroidal Anti-inflammatory Drug/Anti-ulcer Agent Combinations

Overview/Summary

This review will focus on the Nonsteroidal anti-inflammatory drug (NSAID) and anti-ulcer agent combination products. Collectively, these combination products are Food and Drug Administration (FDA)-approved for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis and/or ankylosing spondylitis, while also helping to prevent NSAID-induced gastric or duodenal ulcers.[1-3] NSAIDs inhibit the cyclooxygenase (COX) family of enzymes, preventing the conversion of arachidonic acid to prostaglandin G_2 which is the first step of prostaglandin and thromboxane synthesis. Specifically, the inhibition of the COX-2 isoenzyme appears to be associated with the anti-inflammatory properties of NSAIDs.[4] The NSAID-related gastrointestinal adverse reactions can be severe in some patients and can occur at any time during therapy without warning.[5] All NSAID-containing agents are associated with a Black Box Warning regarding the increased risk of serious gastrointestinal adverse reactions including bleeding, ulceration and perforation of the stomach and intestines, which can be fatal.[5] In an attempt to reduce the occurrence of these ulcers, anti-ulcer agent have been given concomitantly with NSAIDs. Each combination's anti-ulcer component has a distinct mechanism that works to prevent the NSAID-induced ulcers. Misoprostol is a synthetic analog of prostaglandin E_1, which has both gastric antisecretory and mucosal protective properties. NSAIDs decrease the amount of natural prostaglandin E_1 synthesized. By providing a synthetic alternative to the gastric and duodenal mucosa, both bicarbonate and mucus production is increased. In addition, at doses greater than 0.2 mg, misoprostol also has anti-secretory properties.[1] Famotidine is a competitive inhibitor of histamine H_2-receptors. Inhibition of the H_2-receptor results in inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by famotidine, while changes in pepsin secretion are proportional to volume output.[2] Finally, esomeprazole magnesium is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity.[3]

The safety and efficacy of these agents in the prevention of NSAID-induced gastric and/or duodenal ulcers is well documented in several clinical trials.[6-16] Current clinical guidelines published by the American College of Gastroenterology to prevent NSAID-induced ulcers stratify treatment strategy based on cardiovascular and gastrointestinal risk. It is recommended that patients receive an NSAID plus either misoprostol or a PPI if they have low or moderate gastrointestinal risk. If they also have high cardiovascular risk, naproxen is recommended as the NSAID. For patients with high gastrointestinal risk and low cardiovascular risk, a selective COX-2 inhibitor plus a PPI or misoprostol is recommended. Patients with both high gastrointestinal and cardiovascular risk should not receive any type of NSAID therapy. These guidelines also acknowledge that the H_2-receptor antagonists are much less effective compared to misoprostol or a PPI. Adjunctive therapy with standard-dose H_2-receptor antagonists may prevent duodenal ulcers, but it has not been shown to prevent NSAID-related gastric ulceration.[17] Generally, NSAIDs or selective COX-2 inhibitors along with other analgesics such as acetaminophen are considered first line for the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Additional guidelines outlining the specific treatments options for these conditions are outlined in Table 11.[18-23]

Specific agents include Arthrotec® (diclofenac sodium/misoprostol), Duexis® (ibuprofen/famotidine), and Vimovo® (naproxen/esomeprazole magnesium). All combination products have the same drug-interactions, warnings, precautions and black box warning associated with NSAIDs. Differences between products are based on the other agent in the combination and the dosing. Diclofenac sodium/misoprostol is dosed three to four times a day based on indication while ibuprofen/famotidine is dosed three times a day and naproxen/esomeprazole magnesium is dosed only twice daily.[1-3] It is important to note that naproxen/esomeprazole magnesium only carries the indication to prevent gastric ulcers and not duodenal ulcers. Currently, only combination diclofenac sodium/misoprostol is available generically. As single entity agents, all products are available generically, many of which are available over-the-counter.

Medications:

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Diclofenac sodium/misoprostol (Arthrotec®*)	NSAID/Anti-ulcer agents (prostaglandin)	-
Ibuprofen/famotidine (Duexis®)	NSAID/Anti-ulcer agents (H_2-antagonist)	-
Naproxen/esomeprazole magnesium (Vimovo®)	NSAID/Anti-ulcer agents (PPI)	-

H_2=histamine-2 receptor, PPI=proton pump inhibitor
*Generic available in at least one dosage form or strength

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications[1-3]

Indication	Diclofenac/ misoprostol	Ibuprofen/ famotidine	Naproxen/ esomeprazole
For the relief of signs and symptoms of:			
Ankylosing spondylitis			✔
Osteoarthritis	✔	✔	✔
Rheumatoid arthritis	✔	✔	✔
To decrease the risk of developing NSAID-associated ulcers			
Duodenal	✔	✔	
Gastric	✔	✔	✔

NSAID=nonsteroid anti-inflammatory drug

Pharmacokinetics

Table 3. Pharmacokinetics[1-3,24]

Generic Name	Bioavailability (%)	Renal Excretion (%)*	Hepatic Metabolism	Serum Half-Life (hours)
Diclofenac/ misoprostol	Not Reported/ Not Reported	65/80	extensive (CYP2C9, CYP3A4)/ Not reported	2/ 0.33 to 0.66
Ibuprofen/ famotidine	Reported	Not Reported/ 25 to 30	CYP2C9/ minor (Not reported)	4/2
Naproxen/ esomeprazole	95/ Not Reported	95/89	extensive (CYP2C9, CYP1A2)/ extensive (CYP2C9 [primary], 1A2 [secondary])	15/ 1.2 to 1.5

*Reported as changed (<1% unchanged for both)

Clinical Trials

The safety and efficacy of the NSAID/anti-ulcer agent combination products have been evaluated in several clinical trials[1-3,6-16]

Clinical trials have demonstrated that diclofenac sodium/misoprostol has comparable efficacy to that of diclofenac monotherapy for the treatment of osteoarthritis and is associated with a lower rate of gastric and duodenal ulcers.[6]Additionally, the combination agent has demonstrated comparable efficacy to that of naproxen and piroxicam monotherapy for the treatment of osteoarthritis, and is also associated with a lower rate of gastric and duodenal ulcers compared to naproxen, piroxicam, and nabumetone monotherapy.[7,8] In comparison to acetaminophen monotherapy for the treatment of osteoarthritis in terms of efficacy, diclofenac sodium/misoprostol provided statistically significant improvement, but is associated with higher gastrointestinal distress and incidence of adverse events.[9]

The FDA approval of Duexis® (ibuprofen/famotidine) was supported by two phase III clinical trials, REDUCE-1 and REDUCE-2, that enrolled more than 1,500 patients with mild to moderate pain or arthritis. The primary endpoints for REDUCE-1 and REDUCE-2 were the reduction in gastric ulcers during the 24-week treatment period and the reduction in incidence of upper gastrointestinal ulcers during the 24-week period, respectively.[12] Pooled results from both trials indicated that treatment with ibuprofen/famotidine resulted in an absolute risk reduction of 9.6% compared to ibuprofen for the risk of upper gastrointestinal ulcers (95% confidence interval [CI], 5.4 to 13.8). Pooled data also indicated that treatment with ibuprofen/famotidine was associated with an absolute reduction in risk of gastric ulcers and duodenal ulcers (absolute risk reduction [ARR], 7.8%; 95% CI, 3.8 to 11.8 and ARR, 4.0%; 95% CI, 1.9 to 6.1, respectively).[12]

The safety and efficacy of naproxen/esomeprazole magnesium (Vimovo®) in preventing the occurrence of NSAID-induced gastric ulcers was established in two randomized, multi-center, double blind trials (PN400-301 and 302). Both studies evaluated the incidence of gastric ulcer formation in a total of 428 patients taking naproxen/esomeprazole magnesium compared with 426 patients taking enteric-coated naproxen. Patients were at least 18 years of age with a medical condition expected to require daily NSAID therapy for at least six months, and, if less than 50 years old, with a documented history of gastric or duodenal ulcer within the past five years. Approximately 83% of patients were 50 to 69 years of age.[1,13] Both studies showed that naproxen/esomeprazole magnesium 500 mg/20 mg twice daily significantly reduced the 6-month cumulative incidence of gastric ulcers compared to enteric-coated naproxen 500 mg twice daily ($P<0.001$ for both studies). This translated to a relative risk reduction (RRR) of 82.3% and 70.8% in studies 301 and 302, respectively.[1,13] A subgroup analysis that included patients who were concurrently taking low-dose aspirin (≤325 mg daily) was preformed, and the results were consistent with the overall findings of the study. However, the mean duration of therapy was numerically higher for patients who were receiving naproxen/esomeprazole (152 days) compared to patients receiving enteric-coated naproxen alone (124 days).

Additionally, the efficacy of naproxen/esomeprazole magnesium in treating the signs and symptoms of osteoarthritis was established in two 12-week randomized, double-blind, placebo-controlled trials in patients with osteoarthritis of the knee. In both trials, the naproxen/esomeprazole magnesium arm significantly improved baseline scores of the WOMAC pain subscale and the WOMAC physical function subscale and a Patient Global Assessment Score when compared to placebo ($P<0.05$).[1,15]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bocanegra et al[6] (abstract) Diclofenac/misoprostol 50/0.2 MG TID vs diclofenac/misoprostol 75/0.2 mg BID vs diclofenac 75 BID vs placebo	DB, RCT Patients with symptomatic OA of the knee or hip; and a history of GU, DU, or ≥10 erosions	N=572 6 weeks	Primary: Efficacy, incidence of endoscopic upper gastrointestinal ulceration, and safety Secondary: Not reported	Primary: All active treatment groups were significantly better than placebo in improving OA symptoms. There were no significant differences in arthritis efficacy between the diclofenac/misoprostol combination groups and the diclofenac group. Endoscopically diagnosed GUs and/or DUs were significantly less frequent in patients receiving diclofenac/misoprostol 50/0.2 mg (8%), diclofenac/misoprostol 75/0.2 mg (7%), and placebo (4%) compared to diclofenac (17%; P value not reported). Adverse events were not different between the active treatment groups, except for a higher incidence of flatulence with diclofenac/misoprostol 75/0.2 mg and diarrhea with diclofenac/misoprostol 50/0.2 mg. Secondary: Not reported
Agrawal et al[7] Diclofenac/misoprostol 75/0.2 mg BID vs nabumetone 1,500 mg QD vs placebo	DB, MC, PC, PG, RCT Patients with symptomatic OA of the hip or knee with a history of endoscopically confirmed gastric pyloric-channel, or DU, or ≥10 erosions in the stomach or duodenum	N=1,095 6 weeks	Primary: Difference in rate of endoscopically confirmed combined GU and DU at final visit Secondary: Difference of endoscopically confirmed GUs and DUs alone at final visit, rate of combined GUs and DUs based on H. Pylori status	Primary: There was a significantly lower combined incidence of GUs and DUs in the diclofenac/misoprostol group compared to the nabumetone group (4% vs 11%, respectively; P<0.001) at final visit. There was no significant difference in ulceration between the diclofenac/misoprostol group and the placebo group (4% vs 5%, respectively; P=0.525). Secondary: There was a significantly lower incidence of gastric ulceration in the diclofenac/misoprostol group compared with the nabumetone group (1% vs 9%, respectively; P<0.001) and the placebo group (1% vs 4%, respectively; P=0.044) There was no difference in incidence of duodenal ulceration between the diclofenac/misoprostol group and the nabumetone group (4% vs 3%, respectively; P=1.00) and the placebo group (4% vs 1%, respectively; P=0.154). There was no significant differences in combined GU and DU rates based

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				on H. pylori status across treatment groups (P=0.560).
Melo Gomes et al[8] Diclofenac/misoprostol 50/0.2 mg BID vs naproxen 375 mg BID vs piroxicam 10 mg BID	DB, MC, PG, RCT Patients with symptomatic OA of the hip and/or knee, who required continuous NSAID drug therapy for 4 weeks	N=643 4 weeks	Primary: Incidence of gastroduodenal ulcers, GU, and DU on endoscopy after 4 weeks; and change in severity of OA index from baseline to week 4 Secondary: Change from baseline in the physician's global assessment and patient's global assessment of arthritic condition, compliance, and adverse events	Primary: There were significantly fewer gastroduodenal ulcers on endoscopy after four weeks in the diclofenac/misoprostol group compared to the naproxen group (P=0.001) and the piroxicam group (P<0.001). No significant difference was found between the piroxicam and naproxen groups (P=0.56). There were significantly fewer GUs on endoscopy after four weeks in the diclofenac/misoprostol group in comparison to the naproxen group (P=0.004) and the piroxicam group (P=0.007). No significant difference was found between the piroxicam and naproxen groups (P=0.78). There were significantly fewer DUs on endoscopy after four weeks in the diclofenac/misoprostol group compared to the piroxicam group (P=0.002).There was no difference between the naproxen group in comparison to the diclofenac/misoprostol group or the piroxicam group (P values not reported). There was a significantly greater decrease from baseline in the OA severity index at week four in the diclofenac/misoprostol group compared to the piroxicam group (P=0.004).There was no significant difference between the naproxen group and the diclofenac/misoprostol group or the piroxicam group (P values not reported). Secondary: No treatment differences were found in the analyses of change from baseline in the physician's global assessment or patient's global assessment of arthritic condition between all treatment groups (P=0.78 and P=0.27 for overall comparisons, respectively). No significant differences between the three treatment groups in mean compliance with study medication was noted at the final visit (95% in all treatment groups; P value not reported). The incidences of abdominal pain and diarrhea were higher in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				diclofenac/misoprostol group than in the piroxicam group (abdominal pain, 20.8% vs 15.7%, respectively; diarrhea, 18.1% vs 5.5%, respectively; P values not reported) or naproxen group (abdominal pain, 20.8% vs 17.6%, respectively; diarrhea, 18.1% vs 4.8%, respectively; P values not reported).
Pincus et al[9] Diclofenac/misoprostol 75/0.2 mg BID vs APAP 1,000 mg QID	DB, MC, RCT, XO Patients >40 years of age and Kellgren/ Lawrence radiographic grade 2-4 OA of the knee or hip and ≥30 mm pain on a 100-mm VAS	N=227 12 weeks	Primary: Decrease in pain as measured by WOMAC and MHDAQ during two 6 week periods Secondary: Additional measures of pain including: SF-36 scores of pain and physical function, MDHAQ sub scores for ADL and global health, WOMAC sub scores for pain stiffness and function, investigators' assessment of patient global status and change in status, and adverse events	Primary: There was a significantly greater decrease in WOMAC scale rating of the most involved joint from baseline in the diclofenac/misoprostol group in comparison to the APAP group during the first six week period (12.2 from 42.5 vs 6.6 from 44.8, respectively; P=0.011) and the second six week period (12.9 from 40.5 vs 2.1 from 37.4, respectively; P<0.01). There was a significantly greater decrease in MDHAQ VAS pain scores in the diclofenac/misoprostol group in comparison to the APAP group in the first six week period (20.8 from 53.7 vs 13.1 from 53.3; P<0.01) and the second six week period (24.6 from 53.3 vs 0.4 from 45.3; P<0.01). Secondary: Additional efficacy scores including SF-36 pain and physical function scores, MDHAQ scores for basic ADL and global health, WOMAC subscale scores for pain, stiffness, and function and investigators' estimates of patient global status and change in status over six weeks all favored the diclofenac/misoprostol group in comparison to the APAP group (P<0.05 for all values). There was a significantly higher MDHAQ gastrointestinal distress scale score when patients took diclofenac/misoprostol than when patients took APAP across both periods (P=0.013). Any adverse event was reported by a significantly greater number of patients in the diclofenac/misoprostol group compared to the APAP group (54% of 195 patients vs 46% of 205 patients, respectively; P<0.046). Any nonserious adverse gastrointestinal event was more common in the diclofenac/misoprostol group in comparison to the APAP group (34% vs 24%, respectively; P<0.006).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ashworth et al[10] Nabumetone, dosage and frequency not specified vs diclofenac/misoprostol, dosage and frequency not specified vs diclofenac plus a cytoprotective agent dispensed separately, dosage and frequency not specified vs naproxen, dosage and frequency not specified Patients were identified by pharmacy claims and followed for 6 months to determine outcomes.	Cohort study Patients who filled a prescription for any one of the 4 study drugs	N=18,424 6 months	Primary: Estimate the risk of admission to hospital with a primary diagnosis of PUD or gastrointestinal hemorrhage associated with the study drugs Secondary: Not reported	Primary: Crude rates of hospitalization for PUD for diclofenac/misoprostol and nabumetone were significantly lower (0.2% [N=18/8,550] and 0.4% [N=10/2,241], respectively) than those for the diclofenac plus a cytoprotective agent and naproxen (both 1%). Crude rates of hospitalization for gastrointestinal hemorrhage suggest that the rates are lower for nabumetone and diclofenac/misoprostol (0.0% and 0.1%, respectively) compared to diclofenac plus a cytoprotective agent and naproxen (0.3% and 0.2%, respectively); however, this did not reach statistical significance. Compared to diclofenac/misoprostol, the adjusted odds of hospitalization for PUD for patients taking nabumetone was 2.6 (95% CI, 1.0 to 6.6), diclofenac plus a cytoprotective agent 6.8 (95% CI, 3.5 to 13.4), and naproxen 7.9 (95% CI, 3.9 to 15.9). Compared to nabumetone the adjusted odds of hospitalization for PUD for participants taking diclofenac plus a cytoprotective agent was 2.7 (95% CI, 1.2 to 6.0) and for naproxen was 3.1 (95% CI, 1.3 to 7.1). Secondary: Not reported
McKenna (abstract)[11] Diclofenac/misoprostol 50 or 75/0.2 mg, frequency not specified vs	RA Patients with OA, RA, or AS	N=1,824 (first comparison) N=1,459 (second comparison)	Primary: Efficacy and safety Secondary: Not reported	Primary: The efficacy and safety data demonstrate that both strengths of diclofenac/misoprostol are effective anti-inflammatory drugs, with clinical efficacy equivalent to that of diclofenac. Specifically, diclofenac/ misoprostol 50/0.2 mg is at least as effective as ibuprofen, indomethacin, naproxen, or piroxicam

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
diclofenac or ibuprofen AND diclofenac/misoprostol 50/0.2 mg, frequency not specified vs diclofenac, indomethacin, naproxen, or piroxicam For the first comparison, 3 DB, MC, RCTs evaluating the efficacy of the combination diclofenac/misoprostol vs diclofenac or ibuprofen were analyzed. For the second comparison, 4 additional studies assessing antiarthritic efficacy and employing endoscopy to compare the gastroduodenal safety of the combination diclofenac/misoprostol with that of diclofenac, indomethacin, naproxen, or piroxicam were analyzed.		Duration not specified		Both strengths of diclofenac/misoprostol were associated with significantly fewer gastroduodenal ulcers compared with diclofenac. In separate studies, the tolerability of diclofenac/misoprostol 50/200 mg was shown to be equivalent to that of diclofenac, ibuprofen, naproxen, and piroxicam. The tolerability of diclofenac/misoprostol 75/0.2 mg was shown to be equivalent to that of diclofenac. Secondary: Not reported
Laine et al[12]	DB, RCT	N=906	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
REDUCE-1 Ibuprofen/famotidine 800/26.6 mg TID vs ibuprofen 800 mg TID	Patients 40 to 80 years of age requiring daily NSAIDs for ≥6 months with no history of ulcer complications, negative H pylori stool test and baseline endoscopy showing no ulcers and <5 erosions	24 weeks	Gastric ulcers identified at endoscopy during 24-week study period Secondary: Upper gastrointestinal ulcers (gastric and duodenal), duodenal ulcers, gastrointestinal complications (bleeding, ulcer perforation, gastric outlet obstruction due to ulcer)	A greater proportion of patients in the ibuprofen treatment group developed gastric ulcers at week 24 compared to the ibuprofen/famotidine group (22.9 vs 12.7%; P=0.0044; NNT=12). Secondary: Fewer patients treated with ibuprofen/famotidine developed upper gastrointestinal ulcers in both the initial (NNT=9) and post-adjudication analysis (NNT=10) (ARR, 8.5%; 95% CI, 3.2 to 13.8) and fewer patients developed duodenal ulcers (NNT=25) (ARR, 4.1%; 95% CI, 1.2 to 7.0).
Laine et al[12] REDUCE-2 Ibuprofen/famotidine 800/26.6 mg TID vs ibuprofen 800 mg TID	DB, RCT Patients 40 to 80 years of age requiring daily NSAIDs for ≥6 months with no history of ulcer complications, negative H pylori stool test and baseline endoscopy showing no ulcers and <5 erosions	N=627 24 weeks	Primary: Upper gastrointestinal (gastric or duodenal) ulcers identified at endoscopy during the 24-week study period Secondary: Gastric ulcers, duodenal ulcers, gastrointestinal complications (bleeding, ulcer perforation, gastric outlet obstruction due to ulcer)	Primary: A greater proportion of patients in the ibuprofen treatment group developed upper gastrointestinal ulcers compared to the ibuprofen/famotidine group (20.5 vs 13.0%; P=0.0587). Secondary: Fewer patients treated with ibuprofen/famotidine developed gastric ulcers (ARR, 7.8%; 95% CI, 3.8 to 11.8) or duodenal ulcers (ARR, 4.0%; 95% CI, 1.9 to 6.1).
Goldstein et al[13] (PN400-301 and PN400-	AC, DB, MC, PG, RCT	N=854	Primary: Reduction in risk of	Primary: In both studies, the cumulative observed incidence of gastric ulcers over

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
302) Naproxen/esomeprazole 500/20 mg BID vs Naproxen EC 500 mg BID	Patients ≥18 years of age with a medical condition expected to require daily NSAID therapy for at least six months, and, if less than 50 years old a documented history of gastric or duodenal ulcer within the past five years.	6 months (or until gastric ulcer was detected)	endoscopic gastric ulcers over the treatment period in at-risk patients Secondary: Reduction in risk of duodenal ulcers, UGI symptoms, tolerability, safety, and the incidence of gastric ulcers in patients taking concurrent low-dose aspirin	six months was significantly lower in patients treated with naproxen/esomeprazole compared with those treated with EC naproxen (study 301: 4.1% compared to 23.1%, P<0.001; study 302: 7.1% compared to 24.3%, P<0.001). This translated to a RRR of 82.3% and 70.8% in studies 301 and 302, respectively. A significant difference was seen at month 1 and maintained throughout the study Secondary: The incidence of predefined NSAID-associated UGI AEs was significantly lower in the naproxen/esomeprazole groups compared to the EC naproxen groups in both studies (study 301: 52.3% compared to 69.0%, P<0.001; study 302: 54.3% compared to 71.9%, P<0.001). The most common UGI AEs occurring in ≥10% of patients in either the naproxen/esomeprazole or EC naproxen treatment groups respectively of either study were erosive gastritis, gastritis, dyspepsia, and erosive duodenitis. A significantly lower proportion of patients discontinued due to UGI AEs (including duodenal ulcer) in the naproxen/esomeprazole groups compared with the EC naproxen groups (study 301: 3.2% compared to 12.0%, P<0.001; study 302: 4.8% compared to 11.9%, P=0.009). Patients treated with naproxen/esomeprazole reported significantly better UGI tolerability compared with those treated with EC naproxen in terms of SODA scores, proportion of heartburn-free patients, and OTE-DP response in both studies. In all three SODA domains (pain intensity, non-pain symptoms and satisfaction), naproxen/esomeprazole was associated with significantly greater improvements from baseline compared with EC naproxen. Based on a comparison of the distribution of primary OTE-DP responses (better, same or worse), naproxen/esomeprazole was associated with significantly greater improvement in upper abdominal pain and/or discomfort since treatment started relative to EC naproxen in study 301 (P<0.001) and study 302 (P=0.017).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In a pooled analysis of patients taking concurrent low-dose aspirin (≤325 mg/day) from both studies, the cumulative incidence of gastric ulcers was also significantly lower in the naproxen/esomeprazole groups compared to the EC naproxen groups in both the low-dose aspirin users (N=201) and in the low-dose aspirin non-users (N=653). In the safety population, the overall incidence of treatment-emergent AEs was similar between treatment groups in both studies (76.8 to 78.0% compared to 81.5 to 82.8%). The most common treatment-emergent AEs were gastrointestinal disorders, which were more frequent in the EC naproxen groups compared with the naproxen/esomeprazole groups. Common treatment-related AEs included gastritis, erosive gastritis, dyspepsia and erosive duodenitis, reported by ≥10% of patients in either treatment group of either study. A significantly lower proportion of patients treated with naproxen/esomeprazole discontinued from the study as a result of any AE (including duodenal ulcer) compared with those treated with EC naproxen in both studies (study 301: 6.9% compared to 15.7%, P=0.004; study 302: 10.5% compared to 18.1%, P=0.029).
Sostek et al[14] (abstract) Naproxen/esomeprazole 500/20 mg BID	OL, MC Patients ≥50 years of age (or 18 to 49 of age with history of uncomplicated ulcer within the past five years) with a diagnosis of osteoarthritis, rheumatoid arthritis or other condition requiring daily NSAIDs for ≥12 months	N=135 (complete therapy) N=239 (safety population) 12 months	Primary: AEs, vital signs, physical examination, and laboratory tests Secondary: Subgroup analyses included age and low-dose aspirin use, NSAID-associated UGI and cardiovascular AEs	Primary: The incidence of AEs was approximately 70%. The most frequently reported AEs were dyspepsia, constipation, upper respiratory tract infection, nausea, back pain, and contusion (≥5% patients, either population). Treatment-related AEs occurred in 28.0% and 23.7% of patients in the safety and 12-month completer populations, respectively; 18.8% of patients withdrew due to AEs (safety population). Few serious AEs and no deaths occurred. Secondary: In the safety population, AE incidence was 71.4% and 76.9% in patients aged <65 years (N=161) and ≥65 years (N=78), respectively, and 67.6% and 75.8% in low-dose aspirin users (N=74) and non-users (N=165), respectively. Predefined UGI and cardiovascular AEs were observed in 18.8% and 6.3% of patients, respectively, in the safety population, and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				16.3% and 5.2%, respectively, in 12-month completers. Dyspepsia and hypertension were most common.
Hochberg et al (Abstract)[15] and Cryer et al[16] (PN400-307 and PN400-309) Naproxen/esomeprazole 500/20 mg BID vs celecoxib 200 mg QD vs placebo Treatments began being given after an osteoarthritis flare.	AC, DB, MC, PC, PG, RCT Patients ≥50 years of age with symptomatic knee osteoarthritis	N=1,224 12 weeks	Primary: Mean change from baseline to week 12 in WOMAC pain and function subscales, and PGA-VAS scores Secondary: UGI tolerability and safety	Primary: Both naproxen/esomeprazole magnesium and celecoxib were associated with improvements (least squares mean change from baseline to week 12) in WOMAC pain (study 307: -42.0 and -41.8, respectively; study 309: -44.2 and -42.9, respectively), WOMAC function (study 307: -36.4 and -36.3, respectively; Study 309: -38.9 and -36.8, respectively), and PGA-VAS (study 307: 21.2 and 21.6, respectively; study 309: 29.0 and 25.6, respectively; specific P values not reported). A prespecified non-inferiority margin was satisfied for each co-primary endpoint at week 12 in both studies. Significant improvements were observed with naproxen/esomeprazole magnesium versus placebo in both studies (P<0.05). Celecoxib was significantly different from placebo in study 307 (P<0.05); however, the improvements were not significant in study 309. Secondary: Corresponding mean change from baseline to week 12 modified SODA scores were –3.5, –4.8 and –4.0 (study 307), and –4.5, –3.3 and –3.5 (study 309) in the naproxen/esomeprazole, celecoxib, and placebo groups, respectively. The least square mean change in modified SODA scores from baseline to week 12 was also similar in each treatment group. There were no significant differences between naproxen/esomeprazole and celecoxib in study 307 (95% CI, –0.4 to 1.9; P=0.1828) or study 309 (95% CI, –1.8 to 0.6; P=0.2979). Among the subgroup of patients using low-dose aspirin, there were no significant differences between naproxen/esomeprazole and celecoxib at week 12 in either study. The greatest proportion of heartburn-free days between baseline and week 12 was observed in the naproxen/esomeprazole treatment groups of both studies. Patients in the naproxen/esomeprazole treatment group experienced a significantly greater proportion of heartburn-free days over 12 weeks compared with those treated with celecoxib in study 307 (95% CI, 2.1 to 12.7) and study 309 (95% CI, 2.5 to 13.4).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The proportion of patients in study 307 using rescue antacid was significantly lower in the naproxen/esomeprazole magnesium treatment group versus the celecoxib treatment group (95% CI, –21.1 to –3.5). In study 309, there was no significant difference between the two groups The overall proportion of patients reporting predefined NSAID-associated UGI AEs was 17.3% in study 307 and 20.3% in study 309. The incidence was similar between treatment groups in both studies. The most common (reported by at least 3% of patients in any treatment group of either study) were dyspepsia, nausea, upper abdominal pain, and vomiting. Across both studies, the proportion of patients who discontinued as a result of UGI AEs was less than 4%.

Drug regimen abbreviations: BID=twice daily, QD=daily, QID=four times a day, TID=three times a day
Study abbreviations: AC=active control, ARR=absolute risk reduction, CI=confidence interval, DB=double blind, DD=double-dummy, MC=multicenter, NNT=number needed to treat, OL=open label, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial, RRR=relative risk reduction, XO=crossover study
Miscellaneous abbreviations: AE=adverse event, APAP=acetaminophen, AS=ankylosing spondylitis, DU=duodenal ulcer, EC=enteric coated, GU=gastric ulcer, MDHAQ=Multidimensional Health Assessment Questionnaire, NSAID=non-steroidal antiinflammatory drug, OA=osteoarthritis, OTE-DP=Overall Treatment Evaluation-Dyspepsia, PGA-VAS= Patient Global Assessment of osteoarthritis using a visual analog scale, PUD=peptic ulcer disease, RA=rheumatoid arthritis, SODA=Severity of Dyspepsia Assessment UGI=upper gastrointestinal, UGI=upper gastrointestinal, VAS=visual analog scale, WOMAC=Western Ontario and McMaster Osteoarthritis Index

Special Populations

Table 5. Special Populations[1-3]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Diclofenac sodium/ misoprostol	No dosage adjustment required in the elderly. Safety and efficacy has not been established in children <18 years of age.	Not recommended in patients with advanced renal disease.	Dosage adjustment may be required.	X	Yes (% not reported).
Ibuprofen/ famotidine	Safety and efficacy in elderly patients have not been established. Safety and efficacy has not been established in children <18 years of age.	Not recommended for use in patients with a creatinine clearance <50 mL/minute.	Not studied in hepatic dysfunction.	C	Yes (percent unknown)
Naproxen/ esomeprazole	No meaningful differences in efficacy or safety were observed between elderly patients and younger adult patients. Safety and efficacy has not been established in children <18 years of age.	Not recommended in patients with advanced renal disease.	Monitor patients with mild to moderate hepatic impairment closely. Do not use in patients with severe hepatic dysfunction.	C	Likely; use with caution

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-3,24]

Indication	Diclofenac/ misoprostol	Ibuprofen/ famotidine	Naproxen/ esomeprazole
Cardiovascular System			
Hypertension	-	3	-
Central Nervous System			
Headache	-	3	-
Gastrointestinal System			
Abdominal pain	21	-	-
Abdominal pain, upper	-	-	6
Constipation	-	4	-
Diarrhea	19	5	6

Dyspepsia	14	-	8 to 18
Flatulence	9	-	-
Gastric ulcer	-	-	6
Gastritis	-	-	17
Gastritis erosive	-	-	19
Indigestion	-	5	-
Nausea	11	6	5
Urinary System			
Elevated serum creatinine	-	2 to 4	-
Respiratory System			
Upper respiratory infection	-	4	5

- Event not reported or incidence <5%.

Contraindications

Table 7. Contraindications[1-3]

Contraindication	Diclofenac/ misoprostol	Ibuprofen/ famotidine	Naproxen/ esomeprazole
Asthma, urticaria or allergic reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs	✔	✔	✔
Gastrointestinal bleed (active)	✔		
Hypersensitivity to the drug or any inactive ingredient	✔		✔
Hypersensitivity to H2-receptor antagonists		✔	
Hypersensitivity to prostaglandins	✔		
Pregnancy, all stages	✔		
Pregnancy, late stages		✔	
Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery	✔	✔	✔

Black Box Warning for Arthrotec® (diclofenac sodium/misoprostol)[1]

WARNING

ARTHROTEC® CONTAINS DICLOFENAC SODIUM AND MISOPROSTOL. ADMINISTRATION OF MISOPROSTOL TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN MISOPROSTOL WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY. ARTHROTEC SHOULD NOT BE TAKEN BY PREGNANT WOMEN.

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS. ARTHROTEC should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of developing gastric or duodenal ulceration or for developing complications from gastric or duodenal ulcers associated with the use of the NSAID. In such patients, ARTHROTEC may be prescribed if the patient:

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- will begin ARTHROTEC only on the second or third day of the next normal menstrual period.

Cardiovascular Risk

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction,

WARNING
and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. NSAIDs are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery **Gastrointestinal Risk** NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Black Box Warning for Duexis® (ibuprofen/famotidine) and Vimovo® (naproxen/esomeprazole magnesium)[2,3]

WARNING
Cardiovascular Risk NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. NSAIDs are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery **Gastrointestinal Risk** NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Warnings/Precautions

Table 8. Warnings and Precautions[1-3]

Warnings/Precaution	Diclofenac/ misoprostol	Ibuprofen/ famotidine	Naproxen/ esomeprazole
Active bleeding; when active and clinically significant bleeding occurs, treatment should be withdrawn.	✔	✔	✔
Acute interstitial nephritis has been observed with PPI use; discontinue if interstitial nephritis develops.			✔
Anaphylaxis; anaphylaxis may occur in patients without known prior exposure and is not recommended in patients with the aspirin triad (e.g., severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs).	✔	✔	✔
Anemia; anemia has been observed in patients receiving NSAIDs. Patients receiving long-term treatment should have their hemoglobin or hematocrit checked if they exhibit signs or symptoms of anemia.	✔	✔	✔
Aseptic Meningitis has been reported	✔	✔	✔
Bone fractures may be increased in patients who take PPIs; use low doses for the shortest amount of time possible.			✔
Cardiovascular thrombotic events; clinical trials suggest	✔	✔	✔

increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke. Use the lowest effective dose for the shortest duration possible.			
Clostridium difficile associated diarrhea; PPIs may increase the risk, especially in hospitalized patients; use with caution			✔
Concomitant clopidogrel use; avoid due to decreased activity of clopidogrel (decreased metabolism to active-prodrug)			✔
Concomitant methotrexate use with PPIs may increase methotrexate levels leading to toxicity; temporarily withdraw PPI therapy when taking high-dose methotrexate.			✔
Concomitant NSAID use; concomitant use of NSAIDs, including aspirin, may increase the risk of adverse events. Do not use with other NSAIDs.	✔	✔	✔
Concomitant St. John's Wort and Rifampin; concentration of esomeprazole may be decreased; avoid use together			✔
Congestive heart failure and edema; fluid retention and edema have been observed in some patients taking NSAIDs. Use with caution in patients with fluid retention or heart failure.	✔	✔	✔
Corticosteroid treatment; does not substitute for corticosteroids or to treat corticosteroid insufficiency. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if discontinuing therapy and should be closely observed for evidence of adverse effects.	✔	✔	✔
Cyanocobalamin (vitamin B-12) deficiency; daily therapy with acid-reducing therapy may lead to malabsorption of B-12; use with caution long term		✔	✔
Gastrointestinal ulceration, bleeding and perforation; NSAIDs can cause serious gastrointestinal adverse reactions, including inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine. Use with extreme caution in patients with a history of ulcer disease or gastrointestinal bleeding. Use the lowest effective dose for the shortest duration possible.	✔	✔	✔
Hepatic injury; borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs. These laboratory abnormalities may progress, remain unchanged or may be transient with continuing therapy. Treatment should be discontinued if clinical signs and symptoms of liver disease develop.	✔	✔	✔
Hepatic porphyria; avoid use in patients with this condition	✔		
Hypertension; NSAIDs can lead to the onset of new hypertension or worsening or pre-existing hypertension. Use with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of treatment and throughout the course of therapy.	✔	✔	✔
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at			✔

least three months, in most cases after a year of therapy.			
Inhibition of platelet aggregation; NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Patients who may be adversely affected by alterations in platelet function (e.g., patients with coagulation disorders or patients receiving anticoagulants) should be closely monitored.		✔	✔
Masking of inflammation and fever; the pharmacological activity in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.	✔	✔	✔
Pre-existing asthma; the use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm. Since cross-reactivity between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, do not administer to patients with this form of aspirin sensitivity and should be used in caution in patients with pre-existing asthma.	✔	✔	✔
Pregnancy; NSAIDs may cause premature closure of the ductus arteriosus. Starting at 30 weeks gestation, avoid use during pregnancy	✔	✔	✔
Renal injury; long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been observed in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. If clinical signs and symptoms consistent with renal disease develop, therapy should be discontinued.	✔	✔	✔
Seizures have been reported with famotidine use		✔	
Skin reactions; NSAIDs can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis. Treatment should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.	✔	✔	✔
Visual disturbances (blurred and/or diminished vision, scotomata and/or changes in color vision have been reported.		✔	

NSAID=nonsteroidal anti-inflammatory drug, PPI=proton pump inhibitor

Drug Interactions

Table 9. Drug Interactions[1-3,25]

Generic Name	Interacting Medication or Disease	Potential Result
NSAIDs (all)	ACE inhibitors	Coadministration may reduce the antihypertensive effect of ACE inhibitors.
NSAIDs (all)	Aminoglycosides	Plasma aminoglycoside concentrations may be elevated.
NSAIDs (all)	Anticoagulants	NSAIDS decreases platelet aggregation and may prolong bleeding time. Additionally, NSAIDs and warfarin have a synergistic effect on gastrointestinal bleeding and patients who use both drugs together have a higher risk of serious gastrointestinal bleeding compared to patients who use

Generic Name	Interacting Medication or Disease	Potential Result
		either drug along.
NSAIDs (all)	Aspirin	Cardioprotective effect of low-dose aspirin may be reduced. Additionally, these two agents are gastric irritants.
NSAIDs (all)	Azole antifungals	NSAID plasma concentrations may be elevated, increasing pharmacologic and adverse reactions. Additionally, itraconazole may lower NSAID plasma levels, reducing the efficacy of the agents.
NSAIDs (all)	Beta-blockers	NSAIDs can reduce the antihypertensive effect.
NSAIDs (all)	Cholestyramine	May delay the absorption of NSAIDs.
NSAIDs (all)	Diuretics	NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients.
NSAIDs (all)	Heparin	Risk of hemorrhagic adverse reactions may be increased.
NSAIDs (all)	Lithium	Increased pharmacologic and toxic effects of lithium.
NSAIDs (all)	Methotrexate	Increased methotrexate toxicity.
NSAIDs (all)	SSRIs	The risk of upper gastrointestinal bleeding may be increased.
PPIs (all)	Azole antifungals	Plasma levels of certain azole antifungals may be reduced, decreasing the pharmacologic effect.
PPIs (all)	Clopidogrel	The antiplatelet activity of clopidogrel may be decreased.
PPIs (all)	Protease inhibitors	The antiviral activity of certain protease inhibitors may be reduced. Saquinavir plasma levels may be increased.
PPIs (esomeprazole, lansoprazole)	Clarithromycin	Plasma levels of PPIs may be elevated.
Naproxen/ esomeprazole	Probenecid	Given together increases naproxen anion plasma levels and extends its plasma half-life significantly.

ACE=angiotensin converting enzyme, NSAID=nonsteroidal anti-inflammatory drug, PPI=proton pump inhibitor SSRI=selective serotonin reuptake inhibitors

Dosage and Administration

Arthrotec® (diclofenac sodium/misoprostol), Duexis® (ibuprofen/famotidine) and Vimovo® (naproxen/esomeprazole magnesium) are currently only available as tablets, and must be swallowed whole; do not split, chew, crush or dissolve the tablets. It is recommended to use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.[1-3]

Table 10. Dosing and Administration[1-3]

Generic Name	Adult Dose	Pediatric Dose	Availability
diclofenac/ misoprostol	Relief of signs and symptoms of osteoarthritis, and to decrease the risk of developing duodenal or gastric ulcers in patients at risk of developing NSAID-associated ulcers: Tablet: Initial, 50/0.2 mg TID; maximum, 150/0.6 mg/day* Relief of signs and symptoms of rheumatoid arthritis, and to decrease the risk of developing duodenal or gastric ulcers in patients at risk of developing NSAID-associated ulcers: Tablet: Initial, 50/0.2 mg TID or QID;	Safety and efficacy has not been established in children <18 years of age.	Tablet, delayed-release: 50/0.2 mg 75/0.2 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	maximum, 200/0.8 mg/day* Alternative regimens recommended for intolerance*: Tablet: 75 mg/0.2 mg BID or 50/0.2 mg BID		
ibuprofen/ famotidine	Relief of signs and symptoms of osteoarthritis, and to decrease the risk of developing duodenal or gastric ulcers in patients at risk of developing NSAID-associated ulcers: Tablet: Initial, maintenance, maximum, 800/26.6 mg TID	Safety and efficacy has not been established in children <18 years of age.	Tablet, 800/26.6 mg
Naproxen/ esomeprazole	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: Tablet: Initial, maintenance, maximum, 375/20 to 500/20 mg BID 30 minutes before a meal	Safety and efficacy has not been established in children <18 years of age.	Tablet, delayed-release: 375/20 mg 500/20 mg

BID=Twice-daily, NSAID=nonsteroidal anti-inflammatory drug, QD=daily, QID=four times a day, TID=three times a day
*Alternative regimens are less effective at preventing ulcers, but are more tolerable

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Gastroenterology: **Guidelines for Prevention of Nonsteroidal Anti-Inflammatory Drug (NSAID)-Related Ulcer Complications (2009)**[17]	• Risk factors for nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal complications include a previous gastrointestinal event (especially if complicated); age; concomitant use of anticoagulants, corticosteroids, or other NSAIDs including low-dose aspirin; high-dose NSAID therapy; and chronic debilitating disorders (especially cardiovascular disease). • Low-dose aspirin is associated with a definite risk for gastrointestinal complications. • *Helicobacter pylori (H pylori)* infection increases the risk of NSAID-related gastrointestinal complications. • A potential advantage of testing for *H pylori* infection and eradicating the infection if positive in patients requiring long-term NSAID therapy exists. Whether co-therapy with a gastroprotective agent is needed after infection eradication depends on individual patients' underlying gastrointestinal risk. • Misoprostol, at doses of 800 µg/day, is very effective in preventing ulcers, and ulcer complications in patients receiving NSAIDs. The use of misoprostol is limited by its gastrointestinal side effects. When given in lower doses its side-effect profile is the same as that of proton pump inhibitors, and it is equally effective. • Proton pump inhibitors significantly reduce gastric and duodenal ulcers and their complications in patients taking NSAIDs or cyclooxygenase (COX)-2 inhibitors.

Clinical Guideline	Recommendations
	• The COX-2 inhibitors are associated with a significantly lower incidence of gastric and duodenal ulcers when compared to traditional NSAIDs. The beneficial effects of COX-2 inhibitors is negated when the patients is taking concomitant low-dose aspirin. Additionally, the usefulness of these agents has also been reduced by their associated myocardial infarction and other thrombotic cardiovascular events. • The lowest possible dose of celecoxib should be used in order to minimize the risk of cardiovascular events. • Although superior to placebo, high-dose histamine 2 receptor antagonists can reduce the risk of NSAID-induced endoscopic peptic ulcers. The histamine 2 receptor antagonists are significantly less effective compared to proton pump inhibitors; however, there is no clinical outcome data to prove that this strategy prevents ulcer complications. • Co-therapy with a standard-dose histamine 2 receptor antagonist may prevent duodenal ulcers but it has not been shown to prevent NSAID-related gastric ulceration. • Enteric coating or buffering of NSAIDs and co-therapy with sucralfate have not been shown to be effective in preventing NSAID-related gastric or duodenal ulceration. • Patients requiring NSAID therapy who are at high risk should receive alternative therapy, or if anti-inflammatory treatment is absolutely necessary, a COX-2 inhibitor, and co-therapy with misoprostol or a high-dose proton pump inhibitor. • Patients at moderate risk can be treated with a COX-2 inhibitor alone or with a traditional nonselective NSAID plus misoprostol or a proton pump inhibitor. • Patients at low risk (no risk factors) can be treated with a nonselective NSAID. • Patients for whom anti-inflammatory analgesics are recommended who also require low-dose aspirin therapy for cardiovascular disease can be treated with naproxen plus misoprostol or a proton pump inhibitor. • Patients at moderate risk who also are at high cardiovascular risk should be treated with naproxen plus misoprostol or a proton pump inhibitor. • Patients at high gastrointestinal and cardiovascular risk should avoid using NSAIDs or coxibs. Alternative therapy should be prescribed in these patients. • All patients regardless of risk status who are about to start long term traditional NSAID therapy should be considered for testing for *H. pylori* and treated, if positive.
American College of Rheumatology: **American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)**[18]	<u>Nonpharmacologic recommendations for the management of hand osteoarthritis</u> • It is recommended that health professionals should: o Evaluate the ability to perform activities of daily living. o Instruct in joint protection techniques. o Provide assistive devices, as needed, to help patients perform activities of daily living. o Instruct in use of thermal modalities. o Provide splints for patients with trapeziometacarpal joint osteoarthritis. <u>Pharmacologic recommendations for the initial management of hand osteoarthritis</u> • It is recommended that health professionals should use one or more of the

Clinical Guideline	Recommendations
	following: o Topical capsaicin. o Topical NSAIDs, including trolamine salicylate. o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors. o Tramadol. • It is conditionally recommend that health professionals should not use the following: o Intraarticular therapies. o Opioid analgesics. • It is conditionally recommend that: o In persons ≥75 years of age should use topical rather than oral NSAIDs. o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. <u>Nonpharmacologic recommendations for the management of knee osteoarthritis</u> • It is strongly recommend that patients with knee osteoarthritis do the following: o Participate in cardiovascular (aerobic) and/or resistance land-based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with knee osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Use medially directed patellar taping. o Wear medially wedged insoles if they have lateral compartment osteoarthritis. o Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. o Participate in tai chi programs. o Be treated with traditional Chinese acupuncture (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). o Be instructed in the use of transcutaneous electrical stimulation (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination

Clinical Guideline	Recommendations
	with strengthening exercises. o Wearing laterally wedged insoles. o Receiving manual therapy alone. o Wearing knee braces. o Using laterally directed patellar taping. <u>Pharmacologic recommendations for the initial management of knee osteoarthritis</u> • It is conditionally recommend that patients with knee osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Topical NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with knee osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. • No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. <u>Nonpharmacologic recommendations for the management of hip osteoarthritis</u> • It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with hip osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Participation in tai chi. o Receiving manual therapy alone. <u>Pharmacologic recommendations for the initial management of hip osteoarthritis</u> • It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with hip osteoarthritis not use the following:

Clinical Guideline	Recommendations
	o Chondroitin sulfate. o Glucosamine. • No recommendation is made regarding the use of the following: o Topical NSAIDs. o Intraarticular hyaluronate injections. o Duloxetine. o Opioid analgesics.
National Institute for Health and Clinical Excellence: **Osteoarthritis: Care and management in adults (2014)**[19]	• This summary will focus on pharmacologic therapy of osteoarthritis <u>Oral Analgesics</u> • Healthcare professionals should consider offering acetaminophen for pain relief in addition to core treatments; regular dosing may be required. Acetaminophen and/or topical NSAIDs should be considered ahead of oral NSAIDs, COX-2 inhibitors or opioids. • If acetaminophen or topical NSAIDs are insufficient for pain relief for people with osteoarthritis, then the addition of opioid analgesics should be considered. Risks and benefits should be considered, particularly in older people. <u>Topical Treatments</u> • Consider topical NSAIDs for pain relief in addition to core treatments for people with knee or hand osteoarthritis. Consider topical NSAIDs and/or acetaminophen ahead of oral NSAIDs, COX-2 inhibitors or opioids. • Topical capsaicin should be considered as an adjunct to core treatments for knee or hand osteoarthritis. • Do not offer rubefacients for treating osteoarthritis. <u>NSAIDs and Highly-Selective COX-2 Inhibitors</u> • Although NSAIDs and COX-2 inhibitors may be regarded as a single drug class of 'NSAIDs', these recommendations use the two terms for clarity and because of the differences in side-effect profile. • Where acetaminophen or topical NSAIDs are ineffective for pain relief for people with osteoarthritis, then substitution with an oral NSAID/COX-2 inhibitor should be considered. • Use oral NSAIDs/COX-2 inhibitors at the lowest effective dose for the shortest possible period of time. • When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor (other than etoricoxib 60 mg). In either case, co-prescribe with a proton pump inhibitor (PPI), choosing the one with the lowest acquisition cost. • All oral NSAIDs/COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors. • If a person with osteoarthritis needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a PPI) if pain relief is ineffective or insufficient. <u>Intra-Articular Injections</u> • Intra-articular corticosteroid injections should be considered as an adjunct

Clinical Guideline	Recommendations
	to core treatments for the relief of moderate to severe pain in people with osteoarthritis. • Do not offer intra-articular hyaluronan injections for the management of osteoarthritis.
American Academy of Orthopedic Surgeons: **Treatment of Osteoarthritis of the Knee (2013)**[20]	Nonpharmacological/surgical therapy • Patients with symptomatic osteoarthritis of the knee should participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education. • Patients with osteoarthritis of the knee should engage in physical activity consistent with national guidelines. • Weight loss is suggested for patients with symptomatic osteoarthritis of the knee and a body mass index of ≥25. • Acupuncture is not recommended in patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against manual therapy in patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against the use of a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee. • It is suggested that lateral wedge insoles not be used for patients with symptomatic medial compartment osteoarthritis of the knee. • Glucosamine and chondroitin is not recommended for patients with symptomatic osteoarthritis of the knee. Pharmacological therapy • Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee. • Patients with symptomatic osteoarthritis of the knee should receive oral or topical NSAIDs or tramadol. • There is a lack of compelling evidence to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against the use of intraarticular corticosteroids for patients with symptomatic osteoarthritis of the knee. • Patients with symptomatic osteoarthritis of the knee should not use hyaluronic acid. • There is a lack of compelling evidence to recommend for or against the use of growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.
American College of Rheumatology: **2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic**	Initiating and switching among disease-modifying antirheumatic drugs (DMARDs) • If a patient deteriorates from low to moderate/high disease activity after three months of DMARD monotherapy (in patients without poor prognostic features), then methotrexate, hydroxychloroquine, or leflunomide should be added. • Add another non-methotrexate DMARD or switch to a different non-methotrexate DMARD if the patient still experiences moderate or high disease activity following three months of methotrexate or

Clinical Guideline	Recommendations
Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis (2012)[21]	methotrexate/DMARD combination therapy. Switching from DMARDs to biologic agents • For patients with continued moderate or high disease activity following three months of methotrexate monotherapy or DMARD combination therapy, an alternative to DMARD therapy is adding or changing therapy to a TNF-α inhibitor, abatacept or rituximab. • Add or switch to a TNF-α inhibitor if a patient continues to have moderate or high disease activity, following three months of intensified DMARD combination therapy or after a second DMARD has been tried. Switching among biologic agents due to lack of benefit or loss of benefit • In patients with moderate or high disease activity despite three months of TNF-α inhibitor therapy and this is due to a lack or loss of benefit, switching to another TNF-α inhibitor or a non-TNF-α inhibitor biologic is recommended. • In patients with moderate or high disease activity despite six months of a non-TNF-α inhibitor biologic and the failure is due to a lack or loss of benefit, the patient should switch to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. Switching among biologic agents due to harms/adverse events • Patients with high disease activity following treatment failure of a TNF-α inhibitor due to a serious adverse event, an attempt should be made to switch to a non-TNF-α inhibitor biologic. • In patients with moderate or high disease activity after failing an TNF-α inhibitor because of a nonserious adverse event, switch to another anti-TNF-α inhibitor or a non-TNF-α inhibitor biologic. • Patients with moderate or high disease activity after failing a non-TNF-α inhibitor biologic because of an adverse event (serious or nonserious) should be switched to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. Biologic use in Hepatitis B or C • Etanercept could potentially be used in rheumatoid arthritis patients with hepatitis C requiring rheumatoid arthritis treatment; however, biologic agents should not be used in rheumatoid arthritis patients with untreated chronic hepatitis B and in rheumatoid arthritis patients with treated chronic hepatitis B with Child-Pugh class B and higher. Malignancies • Patients treated for solid malignancies more than five years ago or who have been treated for nonmelanoma skin cancer more than five years ago, treatment with a biologic agent may be initiated or continued if the patient would otherwise qualify for biologic therapy. • Rituximab should only be started or initiated in rheumatoid arthritis patients with a previously treated solid malignancy within the last five years, a previously treated nonmelanoma skin cancer within the last five years, a previously treated melanoma skin cancer, or a previously treated lymphoproliferative malignancy. • Little is known about the effects of biologic therapy in patients with a history of a solid cancer within the past five years.

Clinical Guideline	Recommendations
	Congestive heart failure • Anti-TNF biologic in rheumatoid arthritis patients with congestive heart failure is not recommended in those with a New York Heart Association class III or IV and who have an ejection fraction of 50% or less.
National Institute for Health and Clinical Excellence: **Rheumatoid Arthritis: The Management of Rheumatoid Arthritis in Adults (2009)**[22]	• In people with newly diagnosed active rheumatoid arthritis, offer a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within three months of the onset of persistent symptoms. • In people with newly diagnosed rheumatoid arthritis for whom combination DMARD therapy is not appropriate, start DMARD monotherapy; placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD. • When introducing new drugs to improve disease control into the treatment regimen of a person with established rheumatoid arthritis, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled. • Offer short-term treatment with glucocorticoids for managing flares in people with recent onset or established disease, to rapidly decrease inflammation. • In people with established rheumatoid arthritis, only continue long-term treatment with glucocorticoids when the long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological drugs) have been offered. • On the balance of its clinical benefits and cost-effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study; patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. • The anti-TNF agents adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics: o Active rheumatoid arthritis as measured by disease activity score (DAS 28) >5.1 confirmed on at least two occasions, one month apart. o Have undergone trials of two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of six months, with two months at standard dose, unless significant toxicity has limited the dose or duration of treatment. • Anti-TNF agents should be used in combination with methotrexate. Adalimumab or etanercept may be given as monotherapy in patients with intolerance or contraindication to methotrexate. • After initial response, treatment should be monitored no less frequently than six-monthly intervals with assessment of DAS 28. Treatment should be withdrawn if an adequate response is not maintained. • An alternative anti-TNF agent may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial six-month assessment of efficacy. • Escalation of dose of the anti-TNF agents above their licensed starting dose is not recommended. • Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules. • Use of the anti-TNF agents for the treatment of severe, active and

Clinical Guideline	Recommendations
	progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended. • Initiation of anti-TNF agents and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.
Assessment of Spondyloarthritis International Society/European League Against Rheumatism: **2010 Update of the Assessment of Spondyloarthritis International Society/European League Against Rheumatism Recommendations for the Management of Ankylosing Spondylitis (2010)**[23]	• Treatment of ankylosing spondylitis (AS) should be tailored according to: o Current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs). o Level of current symptoms, clinical findings, and prognostic indicators (disease activity/inflammation, pain, function [disability, handicap], structural damage [hip involvement, spinal deformities]. o General clinical status (age, sex, comorbidity, concomitant drugs). o Wishes and expectations of the patient. • Disease monitoring of patients with AS should include: patient history, clinical parameters, laboratory tests, and imaging, all according to the clinical presentation, as well as the Assessment of Spondyloarthritis International Society core set. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and drug treatment. • Optimal management of AS requires a combination of non-pharmacological and pharmacological treatments. • Non-pharmacological treatment of AS should include patient education and regular exercise. Physical therapy with supervised exercises, individually or in a group preferred. Patient associations and self help groups may be useful. • Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors, are recommended as first line drug treatment for patients with AS with pain and stiffness. Continuous treatment with an NSAID is preferred for patients with persistently active, symptomatic disease. Cardiovascular, gastrointestinal and renal risks should be taken into account. • Analgesics, such as opioids and paracetamol, might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated. • Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. The use of systemic corticosteroids for axial disease is not supported by evidence. • There is no evidence for the efficacy of disease modifying antirheumatic drugs (DMARDs), including methotrexate and sulfasalazine, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis. • Anti-tumor necrosis factor α (TNF-α inhibitor) treatment should be given to patients with persistently high disease activity despite conventional treatments according to the Assessment of Spondyloarthritis International Society recommendations. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, TNF-α inhibitor treatment in patients with axial disease. There is no evidence to support a different efficacy of the various TNF-α inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of inflammatory bowel disease a difference in gastrointestinal efficacy needs to be taken into consideration. Switching to a second TNF-α inhibitor might be beneficial, especially in patients that have lost response. There is no evidence to support biologic agents other than TNF-α inhibitor in AS.

Clinical Guideline	Recommendations
	• Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal corrective osteotomy may be considered in patients with severe disabling deformity. A spinal surgeon should be consulted in patients with AS and an acute vertebral fracture.

Conclusions

Collectively, the NSAID/anti-ulcer agent combination products include Arthrotec® (diclofenac sodium/misoprostol), Duexis® (ibuprofen/famotidine) and Vimovo® (naproxen/esomeprazole magnesium). These combination products are FDA-approved for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis and/or ankylosing spondylitis while also helping to prevent NSAID-induced gastric or duodenal ulcers.[1-3] The NSAID is used to treat pain and inflammation associated with these conditions, while the anti-ulcer works to prevent gastric or duodenal ulceration, a common adverse effect of chronic NSAID therapy. While all NSAIDs share the same mechanism of action, each combination's anti-ulcer component is distinct in the way it works to prevent ulcers. All agents in this class are tablets and share the same drug-interactions, warnings, precautions and black box warning associated with NSAIDs but differ based on their anti-ulcer component, particularly dosing. Diclofenac sodium/misoprostol is dosed three to four times a day based on indication while ibuprofen/famotidine is dosed three times a day and naproxen/esomeprazole magnesium is dosed only twice daily.[1-3] It is important to note that naproxen/esomeprazole magnesium only carries the indication to prevent gastric ulcers and not duodenal ulcers. Currently, only combination diclofenac sodium/misoprostol is available generically. As single entity agents, all products are available generically, many of which are available over-the-counter.

The safety and efficacy of these agents in the prevention of NSAID-induced gastric and/or duodenal ulcers is well documented in several clinical trials.[6-16] Current clinical guidelines published by the American College of Gastroenterology to prevent NSAID-induced ulcers stratify treatment strategy based on cardiovascular and gastrointestinal risk. It is recommended that patients receive an NSAID plus either misoprostol or a PPI if they have low or moderate gastrointestinal risk. If they also have high cardiovascular risk, naproxen is recommended as the NSAID. For patients with high gastrointestinal risk and low cardiovascular risk, a selective COX-2 inhibitor plus a PPI or misoprostol is recommended. Patients with both high gastrointestinal and cardiovascular risk should not receive any type of NSAID therapy. Guidelines also acknowledge that the H_2-receptor antagonists are much less effective compared to misoprostol or a PPI. Adjunctive therapy with standard-dose H_2-receptor antagonists may prevent duodenal ulcers, but it has not been shown to prevent NSAID-related gastric ulceration.[17] Generally, NSAIDs or selective COX-2 inhibitors along with other analgesics such as acetaminophen are considered first line for the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.[18-23]

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