New Drug Overview
Duexis® (ibuprofen/famotidine)

- **Overview/Summary:** The nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly utilized classes of medications and are prescribed for analgesia in a variety of clinical scenarios, as well as in inflammatory conditions such as arthritis and other musculoskeletal disorders.[4] The use of these agents is limited by their association with mucosal injury to the upper gastrointestinal tract, which can lead to hospitalization in some patients.

  In order to minimize the potential risks associated with NSAID therapy, it is recommended that patients at high risk for NSAID-related gastrointestinal complications be identified and that appropriate management strategies to prevent peptic ulcers and the associated complications be implented.[4]

  Duexis® (ibuprofen/famotidine) was Food and Drug Administration (FDA) approved in April 2011 for the treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of gastrointestinal ulcers in patients taking ibuprofen for those indications.[3] Duexis® (ibuprofen/famotidine) is a fixed-dose preparation containing ibuprofen, an NSAID, and famotidine, a competitive inhibitor of histamine 2 receptors. Famotidine exerts its pharmacologic effect through the inhibition of both the concentration and volume of gastric secretion.[3,5]

  Current consensus guidelines support the use of high-dose histamine 2 receptor antagonists to reduce the risk of NSAID-induced endoscopic peptic ulcers, although guidelines do acknowledge that the histamine 2 receptor antagonists are much less effective compared to proton pump inhibitors. It is recommended that patients at moderate to high risk of NSAID-related gastric or duodenal ulceration who require NSAID therapy receive misoprostol or a high-dose proton pump inhibitor.[4]

  The FDA approval of Duexis® (ibuprofen/famotidine) was based on two clinical trials evaluating safety and efficacy in patients 40 to 80 years of age requiring daily NSAIDs for at least six months. In both trials, treatment with ibuprofen/famotidine resulted in fewer gastric ulcers, upper gastrointestinal ulcers and duodenal ulcers compared to treatment with ibuprofen alone.[6]

Table 1. Dosing and Administration[3,5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Ibuprofen/ famotidine	Treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis in patients at high risk of developing NSAID-induced upper gastrointestinal ulcers: Tablet: 26.6/800 mg three times daily	Safety and efficacy in children have not been established.	Tablet: 26.6/800 mg

NSAID=nonsteroidal anti-inflammatory drug

Evidence-based Medicine

- The Food and Drug Administration (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.[6]
- 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.[6]
- In REDUCE-1, treatment with ibuprofen/famotidine resulted in a significant reduction in the incidence of gastric ulcers compared to treatment with ibuprofen alone (12.7 vs 22.9%, respectively; *P*=0.0044).[6]
- In REDUCE-2, treatment with ibuprofen/famotidine resulted in significantly fewer upper gastrointestinal ulcers compared to ibuprofen alone (13.0 vs 20.5%; *P*=0.0587).[6]

- Treatment with ibuprofen/famotidine resulted in fewer upper gastrointestinal ulcers and fewer duodenal ulcers compared to ibuprofen in REDUCE-1, as well as fewer gastric ulcers and fewer duodenal ulcers in REDUCE-2.[6]
- 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%).[6]
- 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).[6]
- The most common adverse reactions that occurred ≥1% more frequently in the ibuprofen/famotidine group included nausea, diarrhea, constipation, upper abdominal pain and headache. The discontinuation rate due to adverse events was similar between treatment groups.[6]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - According to the American College of Gastroenterology, patients at high risk for nonsteroidal anti-inflammatory drugs (NSAIDs)-related gastrointestinal complications include patients who are >60 years of age; receiving high-dose NSAID therapy or concurrent anticoagulants, corticosteroids or other NSAID agents (including aspirin); had a previous gastrointestinal event; and have a chronic debilitating disorder, especially cardiovascular disease.[2,4]
    - The two commonly utilized methods to prevent the development of peptic ulceration and gastric mucosal injury in high risk patients receiving NSAIDs include co-therapy with a gastroprotective (or cytoprotective) agent such as a proton pump inhibitor, a high-dose histamine 2 receptor antagonist, or an exogenous prostaglandin; and the use of a cyclooxygenase (COX)-2 inhibitor instead of a traditional NSAID.[4]
    - Co-therapy with a gastroprotective agent protects the gastric mucosal tissue through different mechanisms depending on the agent utilized, and a selective COX-2 inhibitor will be less likely to inhibit COX-1, thereby limiting the potential for gastric mucosal injury.[2]
    - Current consensus guidelines support the use of high-dose histamine 2 receptor antagonists to reduce the risk of NSAID-induced endoscopic peptic ulcers, although guidelines do acknowledge that the histamine 2 receptor antagonists are much less effective compared to proton pump inhibitors.[4]
    - Adjunctive 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. It is recommended that patients at moderate to high risk of NSAID-related gastric or duodenal ulceration who require NSAID therapy receive misoprostol or a high-dose proton pump inhibitor.[4]

- Other Key Facts:
    - The individual components of Duexis® (ibuprofen/famotidine) are available generically over-the-counter.[5]
    - Famotidine is currently available over-the-counter as a 10 and 20 mg tablet and chewable tablet, while ibuprofen is available as a 100 and 200 mg tablet, chewable tablet, liquid capsule or as an oral suspension.[5]
    - There are several proton pump inhibitors that are available generically, including omeprazole, lansoprazole and pantroprazole.[5]

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New Drug Review
Duexis® (ibuprofen/famotidine)

Overview/Summary

The primary mechanism of action of all nonsteroidal anti-inflammatory drugs (NSAIDs) is through the inhibition of cyclooxygenase (COX), resulting in impaired transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes.[1] The COX enzyme can be subdivided into related isoforms, including COX-1 and COX-2; however, important differences in the regulation and expression of these two enzymes in various tissues exist which are relevant to the mechanism of action of NSAIDs and their associated adverse effect profile. Specifically, the COX-2 enzyme is typically undetectable in most tissue except during states of inflammation; therefore, the anti-inflammatory properties of NSAIDs are associated with the inhibition of COX-2.[1] In contrast, COX-1 is expressed variably in most tissues and regulates normal cell processes including gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function. The inhibition of COX-1 by NSAIDs is thought to be associated with the well-established gastrointestinal adverse reaction profile of these agents, which includes dyspepsia, peptic ulcer disease and bleeding.[2] The NSAID-related gastrointestinal adverse reactions can be severe in some patients and can occur at any time during therapy without warning.[3] 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.[3]

The NSAIDs are one of the most commonly utilized classes of medications and are prescribed for analgesia in a variety of clinical scenarios, as well as in inflammatory conditions such as arthritis and other musculoskeletal disorders.[4] The use of these agents is limited by their association with mucosal injury to the upper gastrointestinal tract, which can lead to hospitalization in some patients. In order to minimize the potential risks associated with NSAID therapy, it is recommended that patients at high risk for NSAID-related gastrointestinal complications be identified and that appropriate management strategies to prevent peptic ulcers and the associated complications be implented.[4] According to the American College of Gastroenterology, patients at high risk for NSAID-related gastrointestinal complications include patients who are >60 years of age; receiving high-dose NSAID therapy or concurrent anticoagulants, corticosteroids or other NSAID agents (including aspirin); had a previous gastrointestinal event; and have a chronic debilitating disorder, especially cardiovascular disease.[2,4] The two commonly utilized methods to prevent the development of peptic ulceration and gastric mucosal injury in high risk patients receiving NSAIDs include co-therapy with a gastroprotective (or cytoprotective) agent such as a proton pump inhibitor, a high-dose histamine 2 receptor antagonist, or an exogenous prostaglandin; and the use of a COX-2 inhibitor instead of a traditional NSAID.[4] Co-therapy with a gastroprotective agent protects the gastric mucosal tissue through different mechanisms depending on the agent utilized, and a selective COX-2 inhibitor will be less likely to inhibit COX-1, thereby limiting the potential for gastric mucosal injury.[2]

Duexis® (ibuprofen/famotidine) was Food and Drug Administration (FDA) approved in April 2011 for the treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of gastrointestinal ulcers in patients taking ibuprofen for those indications.[3] Duexis® (ibuprofen/famotidine) is a fixed-dose preparation containing ibuprofen, an NSAID, and famotidine, a competitive inhibitor of histamine 2 receptors. Famotidine exerts its pharmacologic effect through the inhibition of both the concentration and volume of gastric secretion.[3,5]

Current consensus guidelines support the use of high-dose histamine 2 receptor antagonists to reduce the risk of NSAID-induced endoscopic peptic ulcers, although guidelines do acknowledge that the histamine 2 receptor antagonists are much less effective compared to proton pump inhibitors. Adjunctive 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. It is recommended that patients at moderate to high risk of NSAID-related gastric or duodenal ulceration who require NSAID therapy receive misoprostol or a high-dose proton pump inhibitor.[4]

The FDA approval of Duexis® (ibuprofen/famotidine) was based on two clinical trials evaluating safety and efficacy in patients 40 to 80 years of age requiring daily NSAIDs for at least six months. In both trials, treatment with ibuprofen/famotidine resulted in fewer gastric ulcers, upper gastrointestinal ulcers and duodenal ulcers compared to treatment with ibuprofen alone.[6]

Indications

Duexis® (ibuprofen/famotidine) is Food and Drug Administration (FDA)-approved for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers in patients taking ibuprofen for those indications.[3,5]

Pharmacokinetics

Table 1. Pharmacokinetics[3,5]

Generic Name	Bioavailability (%)	Time to Peak Concentration (hours)	Renal Excretion (%)	Hepatic Metabolism (active metabolites)	Serum Half-Life (hours)
Ibuprofen/ famotidine	Not reported	2.0 and 1.9	25 to 30*	Not reported (s-oxide*)	4 and 2

*Famotidine, only

Clinical Trials

The Food and Drug Administration (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.[6]

In REDUCE-1, treatment with ibuprofen/famotidine resulted in a significant reduction in the incidence of gastric ulcers compared to treatment with ibuprofen alone (12.7 vs 22.9%, respectively; *P*=0.0044). Similarly, in REDUCE-2, treatment with ibuprofen/famotidine resulted in significantly fewer upper gastrointestinal ulcers compared to ibuprofen alone (13.0 vs 20.5%; *P*=0.0587).[6]

In terms of secondary endpoints, treatment with ibuprofen/famotidine resulted in fewer upper gastrointestinal ulcers and fewer duodenal ulcers compared to ibuprofen in REDUCE-1, as well as fewer gastric ulcers and fewer duodenal ulcers in REDUCE-2.[6]

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).[6]

The most common adverse reactions that occurred ≥1% more frequently in the ibuprofen/famotidine group included nausea, diarrhea, constipation, upper abdominal pain and headache. The discontinuation rate due to adverse events was similar between treatment groups.[6]

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Laine et al[6] REDUCE-1 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=906 24 weeks	Primary: 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)	Primary: 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[6] 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).

Drug regimen abbreviations: TID=three times daily
Study abbreviations: ARR=absolute risk reduction, CI=confidence interval, DB=double blind, NNT=number needed to treat, NSAID=non-steroidal antiinflammatory, RCT=randomized controlled trial

Special Populations

Table 3. Special Populations[3,5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ibuprofen/ famotidine	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Not recommended for use in patients with a creatinine clearance <50 mL/minute.	Not studied in hepatic dysfunction.	C	Yes (percent unknown)

Adverse Drug Events

Table 4. Adverse Drug Events (%)[3,5]

Adverse Event(s)	Ibuprofen/famotidine
Cardiac Disorders	
Hypertension	3
Central Nervous System	
Headache	3
Gastrointestinal	
Constipation	4
Diarrhea	5
Indigestion	5
Nausea	6
Renal	
Elevated serum creatinine	2 to 4
Respiratory	
Upper respiratory infection	4

Contraindications

Table 5. Contraindications[3,5]

Contraindication	Ibuprofen/famotidine
Asthma, urticaria or allergic reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs	✔
History of hypersensitivity to other H_2-receptor antagonists	✔
Late stages of pregnancy	✔
Treatment of perioperative pain in the setting of coronary artery bypass surgery	✔

Black Box Warning for Duexis® (ibuprofen/famotidine)[3,5]

WARNING
Nonsteroidal anti-inflammatory drugs (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, including Duexis® (ibuprofen/famotidine), are contraindicated in the perioperative setting of coronary artery bypass surgery. 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 reactions can occur at any time during use and without warning. Elderly patients are at

WARNING
greater risk of serious gastrointestinal events.

Warnings/Precautions

Table 6. Warnings and Precautions[3,5]

Warning/Precaution	Ibuprofen/famotidine
Active bleeding; when active and clinically significant bleeding occurs, treatment should be withdrawn.	✔
Anaphylaxis; anaphylaxis may occur in patients without known prior exposure to ibuprofen. Ibuprofen/famotidine 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 with ibuprofen/famotidine should have their hemoglobin or hematocrit checked if they exhibit signs or symptoms of anemia.	✔
Aseptic meningitis; aseptic meningitis with fever and coma has been observed on rare occasions in patients treated with ibuprofen who do not have underlying chronic disease. If signs or symptoms of meningitis develop, the possibility of its being related to ibuprofen/famotidine use should be considered.	✔
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.	✔
Concomitant NSAID use; concomitant use of NSAIDs, including aspirin, may increase the risk of adverse events. Ibuprofen/famotidine should not be used with other NSAIDs.	✔
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; famotidine/ibuprofen cannot be expected to 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.	✔
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.	✔
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.	✔
Inhibition of platelet aggregation; NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Patients	✔

Warning/Precaution	Ibuprofen/famotidine
treated with ibuprofen/famotidine 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 of ibuprofen/famotidine 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, ibuprofen/famotidine should not be administered to patients with this form of aspirin sensitivity and should be used in caution in patients with pre-existing asthma.	✔
Pregnancy; ibuprofen/famotidine may cause premature closure of the ductus arteriosus. Starting at 30 weeks gestation, ibuprofen/famotidine should be avoided.	✔
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; central nervous system adverse events including seizures, delirium and coma have been reported with famotidine in patients with moderate to severe renal insufficiency. Ibuprofen/famotidine is not recommended in patients with creatinine clearance <50 mL/minute.	✔
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. If such symptoms develop, ibuprofen/famotidine should be discontinued and the patient should have an ophthalmologic examination.	✔

NSAID=nonsteroidal anti-inflammatory drug

Drug Interactions

Table 7. Drug Interactions[3,5]

Generic Name	Interacting Medication or Disease	Potential Result
Ibuprofen/famotidine	ACE inhibitors	Coadministration of ibuprofen may reduce the antihypertensive effect of ACE inhibitors. Monitor patients if concomitant therapy is necessary.
Ibuprofen/famotidine	Diuretics	Ibuprofen may reduce the natriuretic effect of furosemide and thiazides in some patients secondary to the inhibition of renal prostaglandin synthesis. If concomitant therapy is necessary, patients should be monitored closely for signs of renal failure as well as to assure diuretic efficacy.
Ibuprofen/famotidine	SSRIs	There is an increased risk of gastrointestinal bleeding when SSRIs are taken concomitantly with NSAIDs, including COX-2 selective inhibitors. Monitor patients if

Generic Name	Interacting Medication or Disease	Potential Result
		concomitant therapy is necessary.
Ibuprofen/famotidine	Warfarin-type anticoagulants	Warfarin and NSAIDs 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 either drug along. Caution should be used in patients receiving anticoagulants.
Ibuprofen/famotidine	Aspirin	Coadministration of ibuprofen and aspirin may reduce the protein binding of ibuprofen, thereby increasing the risk of adverse events. Monitor patients if concomitant therapy is necessary.
Ibuprofen/famotidine	Lithium	Concomitant administration of ibuprofen and lithium may result in elevated plasma lithium levels and a reduction in renal clearance of lithium. If concomitant therapy is necessary, patients should be monitored closely for signs of lithium toxicity.
Ibuprofen/famotidine	Methotrexate	NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model, suggesting that concomitant use of NSAIDs may enhance the toxicity of methotrexate. Monitor patients if concomitant therapy is necessary.
Ibuprofen/famotidine	Cholestyramine	Concomitant administration of cholestyramine with NSAIDs may delay the absorption of NSAIDs. Monitor patients for adequate symptom management if concomitant administration is necessary.

ACE=angiotensin converting enzyme, COX=cyclooxygenase, NSAID=nonsteroidal anti-inflammatory drug, SSRI=selective serotonin reuptake inhibitors

Dosage and Administration

Duexis® (ibuprofen/famotidine) is currently available in tablet formulation, only, and must be swallowed whole.[3,5]

Table 8. Dosing and Administration[3,5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Ibuprofen/ famotidine	Treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis in patients at high risk of developing NSAID-induced upper gastrointestinal ulcers: Tablet: 26.6/800 mg three times daily	Safety and efficacy in children have not been established.	Tablet: 26.6/800 mg

NSAID=nonsteroidal anti-inflammatory drug

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Gastroenterology: **Guidelines for Prevention of Nonsteroidal Anti-Inflammatory Drug**	• 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).

Clinical Guideline	Recommendations
(NSAID)-Related Ulcer Complications (2009)[4]	• 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. • 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

Clinical Guideline	Recommendations
	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)**[7]	<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 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

Clinical Guideline	Recommendations
	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 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.

Clinical Guideline	Recommendations
	• 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. Pharmacologic recommendations for the initial management of hip osteoarthritis • 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: 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.
American Academy of Orthopedic Surgeons: **Treatment of Osteoarthritis of the Knee (2013)**[8]	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

Clinical Guideline	Recommendations
	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 Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis (2012)**[9]	<u>Initiating and switching among disease-modifying antirheumatic drugs (DMARDs)</u> • 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 methotrexate/DMARD combination therapy. <u>Switching from DMARDs to biologic agents</u> • 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. <u>Switching among biologic agents due to lack of benefit or loss of benefit</u> • 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. <u>Switching among biologic agents due to harms/adverse events</u> • 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. <u>Biologic use in Hepatitis B or C</u> • Etanercept could potentially be used in rheumatoid arthritis patients with

Clinical Guideline	Recommendations
	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. 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)**[10]	• 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

Clinical Guideline	Recommendations
	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 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.

Conclusions

Treatment with Duexis® (ibuprofen/famotidine) has been shown in two clinical trials to reduce the risk of gastrointestinal complications associated with non-steroidal antiinflammatory drug (NSAID) therapy.[6] Current consensus guidelines support the use of histamine 2 receptor antagonists, such as famotidine, for the prevention of NSAID-related gastrointestinal complications; however, treatment with proton pump inhibitors or misoprostol may be preferred in conjunction with NSAID therapy for patients at moderate to high risk of NSAID-related gastrointestinal complications.[4]

The individual components of Duexis® (ibuprofen/famotidine) are available generically over-the-counter. Famotidine is currently available over-the-counter as a 10 and 20 mg tablet and chewable tablet, while ibuprofen is available as a 100 and 200 mg tablet, chewable tablet, liquid capsule or as an oral suspension. In addition, there are several proton pump inhibitors that are available generically, including omeprazole, lansoprazole and pantroprazole.[5]

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