## FDA APPROVED INDICATIONS AND DOSAGE\(^1,4,6\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dosing and Administration</th>
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<tbody>
<tr>
<td><strong>Duexis</strong> (ibuprofen/ famotidine)</td>
<td>Relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers.</td>
<td>1 tablet three times daily</td>
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<td>800 mg / 26.6 mg tablet</td>
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<tr>
<td><strong>Vimovo</strong> (naproxen/ esomeprazole)</td>
<td>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 Vimovo is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products.</td>
<td>1 tablet twice daily</td>
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<td>375 mg / 20 mg tablet</td>
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<td>500 mg / 20 mg tablet</td>
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<tr>
<td><strong>Yosprala</strong> (aspirin/ omeprazole)</td>
<td>The aspirin component of is indicated for: • Reducing the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, reducing the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris • Reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris • Use in patients who have undergone revascularization procedures (Coronary Artery Bypass Graft [CABG] or Percutaneous Transluminal Coronary Angioplasty [PTCA]) when there is a pre-existing condition for which aspirin is already indicated The omeprazole component of is indicated for decreasing the risk of developing aspirin associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age ((\geq) 55) or documented history of gastric ulcers.</td>
<td>1 tablet daily at least 60 minutes before a meal</td>
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<td>81 mg / 40 mg tablet</td>
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<td>325 mg / 40 mg tablet</td>
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CLINICAL RATIONALE

Strategies for gastroprotection during NSAID therapy include supplementation with a synthetic prostaglandin analog (misoprostol), gastric acid suppression (proton pump inhibitors), or the selective use of those NSAIDs least likely to inhibit gastric prostaglandins.2,3

The Agency for Healthcare Research and Quality 2011 Update Analgesics for Osteoarthritis (an update of the 2006 Comparative Effectiveness Review) states that NSAIDs ibuprofen and diclofenac, but not naproxen, were associated with an increased risk of heart attack when compared with placebo. Adding an H-2 antagonist, misoprostol, or a PPI reduced the risk of endoscopically detected gastric and duodenal ulcers in patients prescribed nonselective NSAIDs. In individuals with increased risk of GI bleeding who were prescribed a nonselective NSAID, adding a PPI resulted in a reduced risk of endoscopically detected duodenal ulcers when compared with misoprostol or H-2 antagonists, a lower risk of endoscopically detected gastric ulcers when compared with H-2 antagonists, and a similar risk of endoscopically detected gastric ulcers when compared with misoprostol.5

Efficacy

Although Vimovo, Duexis, and Yosprala showed statistically significant efficacy over placebo or single NSAID agents, no clinical trials were conducted comparing these combination agents against taking both active ingredients separately but at the same time.1,4,6

Safety

Vimovo is contraindicated in the following:1
- Known hypersensitivity to any component of Vimovo or substituted benzimidazoles
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs
- Use during the perioperative period in the setting of coronary artery bypass graft (CABG) surgery

Vimovo also carries the following black box warning:1
- Naproxen, a component of Vimovo, 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.
- Vimovo is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.
- NSAIDs, including naproxen, a component of Vimovo, 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 (GI) events.

Duexis is contraindicated in the following:4
- Pre-existing asthma, urticaria, or allergic reactions after taking aspirin or other NSAIDs
- Use during the perioperative period in the setting of coronary artery bypass graft surgery
- Starting at 30 weeks gestation, Duexis should not be used by pregnant women as premature closure of the ductus arteriosus in the fetus may occur.
- Known hypersensitivity to other H2 -receptor antagonists

Duexis also carries the following black box warnings:4
- Ibuprofen, a component of Duexis, may increase the risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. Risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
• Duexis is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.
• NSAIDs, including ibuprofen, a component of Duexis, increase the risk of serious gastrointestinal (GI) adverse reactions including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Reactions can occur at any time without warning symptoms. Elderly patients are at greater risk.

Yosprala carries the following contraindications:6
• History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs
• In pediatric patients with suspected viral infections, with or without fever, because of the risk of Reye’s Syndrome
• Known hypersensitivity to aspirin, omeprazole, substituted benzimidazoles or to any of the excipients of Yosprala
• Patients receiving rilpivirine-containing products

For additional clinical information see Prime Therapeutics Formulary Monograph Vimovo (naproxen/esomeprazole) and Prime Therapeutics Formulary Monograph Duexis (ibuprofen/famotidine).

REFERENCES
Combination GI Protectants Step Therapy

OBJECTIVE
The intent of the Combination Gastrointestinal (GI) Protectants Step Therapy (ST) program is to accommodate the use of target agents when the patient has tried all of the ingredients within the target combination agent as separate dosage forms, or the prescriber has provided documentation that the use of the individual ingredients within the target combination agent as separate dosage forms is not clinically appropriate. The program allows for continuation of therapy with the target agent when a patient is currently receiving the target agent.

TARGET AGENTS
- Duexis® (ibuprofen/famotidine)
- Vimovo™ (naproxen/esomeprazole)
- Yosprala™ (aspirin/omeprazole)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Vimovo, Duexis, Yosprala will be approved when ANY ONE of the following is met:
1. The patient’s medication history includes the use of all of the ingredients within the target combination agent as separate dosage forms in the past 90 days
   OR
2. The prescriber has provided documentation that the use of the individual ingredients within the target combination agent as separate dosage forms is not clinically appropriate for the patient
   OR
3. There is documentation that the patient is currently using the requested agent
   OR
4. The prescriber states the patient is currently using the requested agent AND is at risk if therapy is changed

Length of approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.