### Combination Gastrointestinal Protectants

#### Step Therapy Program Summary

This program applies to FlexRx Open, GenRx Open, Health Insurance Marketplace and KeyRx formularies.

This program is a FlexRx standard and GenRx standard step therapy program. The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

### FDA APPROVED INDICATIONS AND DOSAGE

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<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dosing and Administration</th>
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| **Duexis** (ibuprofen/famotidine)  
800 mg / 26.6 mg tablet | Relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers. | 1 tablet three times daily                       |
| **Vimovo** (naproxen/esomeprazole)  
375 mg / 20 mg  
500 mg / 20 mg tablet | 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 | 1 tablet twice daily |
| **Yosprala** (aspirin/omeprazole)  
81 mg / 40 mg  
325 mg / 40 mg tablet | 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 | 1 tablet daily at least 60 minutes before a meal |
for decreasing the risk of developing aspirin associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age (≥ 55) or documented history of gastric ulcers.

**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:

- 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:

- 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.

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

**PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**
**Target Agents** 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

**Length of approval:** 12 months
**Step Therapy Supplement**

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

**STEP THERAPY SUPPLEMENT OBJECTIVE**
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

**CONDITIONS FOR APPROVAL**
The requested agent will be approved when ONE of the following are met:

1. **The patient is currently being treated with the requested agent as indicated by ALL of the following:**
   a. A statement by the prescriber that the patient is currently taking the requested agent
   **AND**
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   **AND**
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm
   **OR**

2. **The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:**
   a. Evidence of a paid claim(s) within the past 999 days
   **OR**
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event
   **OR**

3. **The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm**

**Length of Approval:** As per program specific criteria