

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205103Orig1s000**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YOSPRALA safely and effectively. See full prescribing information for YOSPRALA.

**YOSPRALA (aspirin and omeprazole) delayed-release tablets, for oral use**

**Initial US Approval: 2016**

### -----INDICATIONS AND USAGE-----

YOSPRALA is a combination of aspirin, an anti-platelet agent, and omeprazole, a proton pump inhibitor (PPI), indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers.

The aspirin component of YOSPRALA 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 YOSPRALA 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. (1)

### Limitations of Use:

- Not for use as the initial dose of aspirin therapy during onset of acute coronary syndrome, acute myocardial infarction or before percutaneous coronary intervention. (1)
- Has not been shown to reduce the risk of gastrointestinal bleeding due to aspirin. (1)
- YOSPRALA is not interchangeable with the individual components of aspirin and omeprazole. (1)

### -----DOSAGE AND ADMINISTRATION-----

- Recommended dosage: One tablet daily at least 60 minutes before a meal. (2.1, 2.2)
- Do not split, chew, crush or dissolve the tablet. (2.2)

### -----DOSAGE FORMS AND STRENGTHS-----

Delayed-Release Tablets (3):

- 81 mg delayed-release aspirin/40 mg immediate-release omeprazole
- 325 mg delayed-release aspirin/40 mg immediate-release omeprazole

### -----CONTRAINDICATIONS-----

- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. (4)
- In pediatric patients with suspected viral infections, with or without fever, because of the risk of Reye's Syndrome. (4)
- Known hypersensitivity to aspirin, omeprazole, substituted benzimidazoles or to any of the excipients of YOSPRALA. (4)
- Patients receiving rilpivirine-containing products. (4, 7)

### -----WARNINGS AND PRECAUTIONS-----

- Coagulation Abnormalities: Risk of increased bleeding time with aspirin, especially in patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders. Monitor patients for signs of increased bleeding. (5.1)
- GI Adverse Reactions (including ulceration and bleeding): Monitor for signs and symptoms and discontinue treatment if bleeding occurs. (5.2)

- Bleeding Risk with Use of Alcohol: Avoid heavy alcohol use (three or more drinks every day). (5.3)
- Reduction in Antiplatelet Activity with Clopidogrel due to Interference with CYP2C19 Metabolism: Consider other antiplatelet therapy. (5.4, 7)
- Reduction in Efficacy of Ticagrelor: Avoid use with the 325/40 strength of YOSPRALA. (5.5, 7)
- Renal Failure: Avoid YOSPRALA in patients with severe renal failure. (5.6, 8.6)
- Gastric Malignancy: In adults, response to gastric symptoms does not preclude the presence of gastric malignancy; Consider additional follow-up and diagnostic testing. (5.7)
- Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.8)
- Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk; use lowest dose and shortest duration of treatment. (5.9)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine; use lowest dose and shortest duration of treatment. (5.10)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue YOSPRALA and refer to specialist for evaluation. (5.11)
- Hepatic Impairment: Avoid YOSPRALA in patients with all degrees of hepatic impairment. (5.12, 8.7)
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) of PPI may lead to malabsorption or deficiency. (5.13)
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs; consider monitoring magnesium levels. (5.14)
- Reduced Effect of Omeprazole with St. John's Wort or Rifampin: Avoid concomitant use. (5.15, 7)
- Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increased Chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors; temporarily stop YOSPRALA at least 14 days before assessing CgA levels (5.16, 7)
- Bone Marrow Toxicity with Methotrexate, especially in the elderly or renally impaired: Use with PPIs may elevate and/or prolong serum levels of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate, consider a temporary withdrawal of YOSPRALA. (5.17, 7)
- Premature closure of the ductus arteriosus: Avoid use in pregnant women starting at 30 weeks gestation. (5.18, 8.1)

### -----ADVERSE REACTIONS-----

Most common adverse reactions in adults ( $\geq 2\%$ ) are: gastritis, nausea, diarrhea, gastric polyps, and non-cardiac chest pain. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Aralez Pharmaceuticals at 1-866-207-6592 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### -----DRUG INTERACTIONS-----

See full prescribing information for a list of clinically important drug interactions. (7)

### -----USE IN SPECIFIC POPULATIONS-----

- Lactation: Breastfeeding not recommended. (8.2)
- Females and Males of Reproductive Potential Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of YOSPRALA in women who have difficulties conceiving. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

YOSPRALA, a combination of aspirin and omeprazole, is indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers.

The aspirin component of YOSPRALA 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 YOSPRALA 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.

#### Limitations of Use:

- YOSPRALA contains a delayed-release formulation of aspirin and it is not for use as the initial dose of aspirin therapy during onset of acute coronary syndrome, acute myocardial infarction or before percutaneous coronary intervention (PCI), for which immediate-release aspirin therapy is appropriate.
- YOSPRALA has not been shown to reduce the risk of gastrointestinal bleeding due to aspirin.
- YOSPRALA is not interchangeable with the individual components of aspirin and omeprazole.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

- Take one tablet daily.
- YOSPRALA is available in combinations that contain 81 mg or 325 mg of aspirin. Generally 81 mg of aspirin has been accepted as an effective dose for secondary cardiovascular prevention. Providers should consider the need for 325 mg and refer to current clinical practice guidelines.

#### 2.2 Administration Instructions

- Take YOSPRALA once daily at least 60 minutes before a meal.
- The tablets are to be swallowed whole with liquid. Do not split, chew, crush or dissolve the tablet.

- Use the lowest effective dose of YOSPRALA based on the individual patient's treatment goals and to avoid potential dose dependent adverse reactions including bleeding.
- If a dose of YOSPRALA is missed, advise patients to take it as soon as it is remembered. If it is almost time for the next dose, skip the missed dose. Take the next dose at the regular time. Patients should not take 2 doses at the same time unless advised by their doctor.
- Do not stop taking YOSPRALA suddenly as this could increase the risk of heart attack or stroke.

### 3 DOSAGE FORMS AND STRENGTHS

Oval, blue-green, film-coated, delayed-release tablets for oral administration containing either:

- 81 mg delayed-release aspirin and 40 mg immediate-release omeprazole, printed with 81/40, or
- 325 mg delayed-release aspirin and 40 mg immediate-release omeprazole, printed with 325/40.

### 4 CONTRAINDICATIONS

YOSPRALA is contraindicated in:

- Patients with known allergy to aspirin and other nonsteroidal anti-inflammatory drug products (NSAIDs) and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).
- Pediatric patients with suspected viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.
- YOSPRALA is contraindicated in patients with known hypersensitivity to aspirin, omeprazole, substituted benzimidazoles, or to any of the excipients in the formulation [*see Warnings and Precautions (5.8), Adverse Reactions (6.2)*].
- Proton pump inhibitor (PPI)-containing products, including YOSPRALA, are contraindicated in patients receiving rilpivirine-containing products [*see Drug Interactions (7)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Coagulation Abnormalities

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders. Monitor patients for signs of increased bleeding.

#### 5.2 Gastrointestinal Adverse Reactions

Aspirin is associated with serious gastrointestinal (GI) adverse reactions, including inflammation, bleeding ulceration and perforation of the upper and lower GI tract. Other adverse reactions with aspirin include stomach pain, heartburn, nausea, and vomiting.

Serious GI adverse reactions reported in the clinical trials of YOSPRALA were: gastric ulcer hemorrhage in one of the 521 patients treated with YOSPRALA and duodenal ulcer hemorrhage in one of the 524 patients treated with enteric-coated aspirin. In addition, there

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