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 (≥ 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)
- Do not substitute YOSPRALA with the single-ingredient products 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)

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)
- Abnormal Laboratory Tests: Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time. (5.19)
- Fundic Gland Polyps: Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy. (5.20)

-------------------------------**ADVERSE REACTIONS**---------------------------
Most common adverse reactions in adults (≥ 2%) are: gastritis, nausea, diarrhea, gastric polyps, and non-cardiac chest pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharm-Olam at 1-866-511-6754 or FDA at 1-800-FDA-1088 or 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.

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

- 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 (≥ 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.
- Do not substitute YOSPRALA with the single-ingredient products 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:

- 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 were two cases of intestinal hemorrhage, one in each treatment group, and one patient treated with YOSPRALA experienced obstruction of the small bowel.

Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, monitor patients for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Inform patients about the signs and symptoms of GI adverse reactions.

If active and clinically significant bleeding from any source occurs in patients receiving YOSPRALA, discontinue treatment.

5.3 Bleeding Risk with Use of Alcohol

Counsel patients who consume three or more alcoholic drinks every day about the bleeding risks involved with chronic, heavy alcohol use while taking YOSPRALA.

5.4 Interaction with Clopidogrel

Avoid concomitant use of YOSPRALA with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as omeprazole, that interfere with CYP2C19 activity. Co-administration of clopidogrel with 80 mg omeprazole reduces the pharmacological activity of clopidogrel, even when administered 12 hours apart. When using YOSPRALA, consider alternative anti-platelet therapy *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

5.5 Interaction with Ticagrelor

Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor in preventing thrombotic cardiovascular events. Avoid concomitant use of ticagrelor with the 325 mg/40 mg tablet strength of YOSPRALA *[see Drug Interactions (7)]*.

5.6 Renal Failure

Avoid YOSPRALA in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute). Regular use of aspirin is associated in a dose-dependent manner with an increased risk of chronic renal failure. Aspirin use decreases glomerular filtration rate and renal blood flow especially with patients with pre-existing renal disease. *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

5.7 Presence of Gastric Malignancy

In adults, response to gastric symptoms with YOSPRALA does not preclude the presence of gastric malignancy. Consider additional gastrointestinal follow-up and diagnostic testing in

Discontinue YOSPRALA and evaluate patients with suspected acute TIN *[see Contraindications (4)]*.

5.9 *Clostridium difficile*-Associated Diarrhea

Published observational studies suggest that PPI-containing therapy like YOSPRALA may be associated with an increased risk of *Clostridium difficile*-associated diarrhea (CDAD), especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve *[*see *Adverse Reactions (6.2)]*.

Use the lowest dose and shortest duration of YOSPRALA appropriate to the condition being treated.

5.10 Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Use the lowest dose and shortest duration of YOSPRALA therapy appropriate to the condition being treated. Manage patients at risk for osteoporosis-related fractures according to established treatment guidelines *[see Adverse Reactions (6.2)]*.

5.11 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including omeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematous cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE), and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly.Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment, but some cases occurred days or years after initiating treatment. SLE occurred primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving YOSPRALA, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serologicial testing (e.g., ANA) may be positive and elevated serologicial test results may take longer to resolve than clinical manifestations.

5.12 Hepatic Impairment

Long-term moderate to high doses of aspirin may result in elevations in serum ALT levels. These abnormalities resolve rapidly with discontinuation of aspirin. The hepatotoxicity of aspirin is usually mild and asymptomatic. Bilirubin elevations are usually mild or absent. Systemic exposure to omeprazole is increased in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*. Avoid YOSPRALA in patients with any degree of hepatic impairment *[see Use in Specific Populations (8.7)]*.

5.13 Cyanocobalamin (Vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing

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