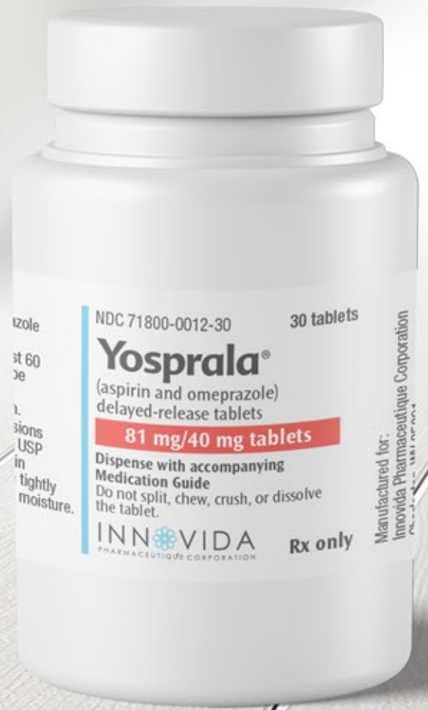
delayed-release tablets

Yosprala®

(aspirin and omeprazole)



Please see Indications and Usage and Important Safety Information thoughout.
Please see enclosed full Prescribing Information.

Important Safety Information

Warnings and Precautions

Cyanocobalamin (Vitamin B12) Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (eg, longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with Yosprala®.

Hypomagnesemia
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take Yosprala with medications such as digoxin or drugs that may cause hypomagnesemia (eg, diuretics), consider monitoring magnesium levels prior to initiation of Yosprala and periodically during treatment.

Reduced Effect of Omeprazole with St. John's Wort or Rifampin
Drugs which induce the CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease concentrations of omeprazole. Avoid concomitant use of Yosprala with St. John's Wort or rifampin.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors
Serum chromogranin A (CgA) levels increase secondary to omeprazole-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic interventions for neuroendocrine tumors. Temporarily discontinue treatment with Yosprala at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (eg, for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Interaction with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In highdose methotrexate administration, a temporary withdrawal of Yosprala may be considered in some patients.

Premature Closure of Fetal Ductus Arteriosus
NSAIDs including aspirin, may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Yosprala, in pregnant women starting at 30 weeks of gestation (third trimester).

Adverse Reactions
Most common adverse reactions in adults (incidence ≥2% and more common in Yosprala™ treated patients) are: gastritis, nausea, diarrhea, gastric polyps, and non-cardiac chest pain. Less common adverse reactions were 2 patients with upper GI bleeding (gastric or duodenal) and 2 patients with lower GI bleeding (hematochezia and large intestinal hemorrhage) and one additional patient experienced obstruction in the small bowel.

Drug Interactions
See the full prescribing information for the complete list of drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with Yosprala and instructions for preventing or managing them.

Use in Specific Populations
- Pregnancy: Use during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of Yosprala in pregnant women starting at 30 weeks of gestation (third trimester)
- Lactation: Breastfeeding not recommended

Indication 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 (≥ 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

To report SUSPECTED ADVERSE EVENTS, contact Innovida Pharmaceutique Corporation at 1-888-202-0649 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Reference: Yosprala Prescribing Information Charleston, WV: Innovida Pharmaceutique Corporation; 2019

Manufactured for: Innovida Pharmaceutique Corporation
1018 Kanawha Blvd. East Suite 200
Charleston, WV 25301

For more information
1-888-202-0649
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www.innovidarx.com

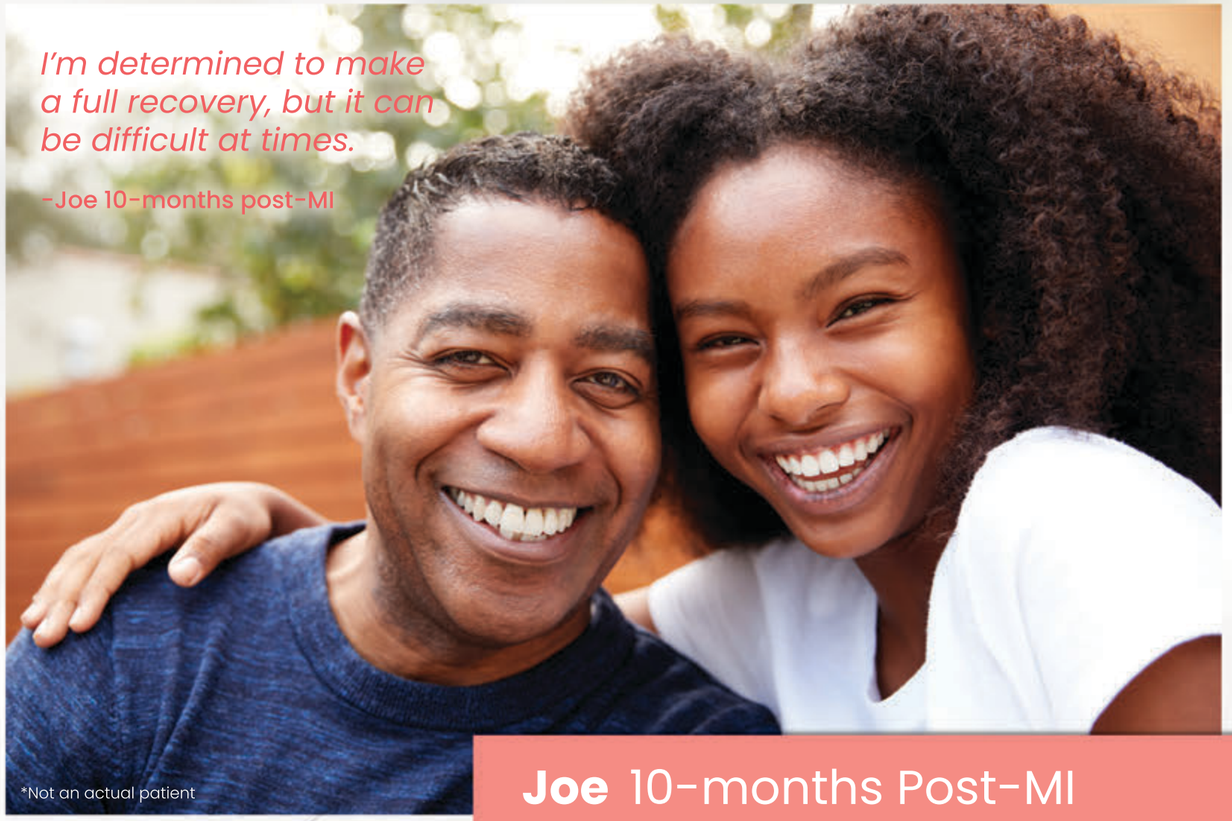
INNOVIDA
PHARMACEUTIQUE CORPORATION

delayed-release tablets

Yosprala®

(aspirin and omeprazole)

Overwhelmed and suffering silence



*Not an actual patient

Joe 10-months Post-MI

- Entertainment attorney and father of 2 college-aged children
- Worked and ate too much - until having a heart attack
- Determined to turn his life around, but having trouble coping with all the changes in his life

Is your patient overwhelmed and at risk for discontinuing aspirin **because of GI symptoms?**

Age: 55 Sex: Male Body Mass Index: 30 kg/m^2

Ethnicity: African American

Medical History:
MI within past year, Received Stent
History of gastric ulcer

Comorbidities:
Diabetes, Hypertension, Hypercholesterolemia

Medication Regimen:
Aspirin + another anti-platelet (DAPT)
Statin, Incretin mimetic, ACE inhibitor
PPI, Beta blocker

Coverage: Commerical

Notes: *Having trouble keeping track of his medications; reports stomach upset that he self-manages by occasionally skipping his aspirin*

If your patients are at risk for discontinuing aspirin treatment due to GI symptoms, talk to them about Yosprala®

Please see Indications and Usage and Important Safety Information thoughout.
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ACE. angiotensin-converting enzyme, **DAPT**. dual antiplatelet therapy.
GI. gastrointestinal, **MI**. myocardial infarction, **PPI**. proton pump inhibitor.

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Yosprala®

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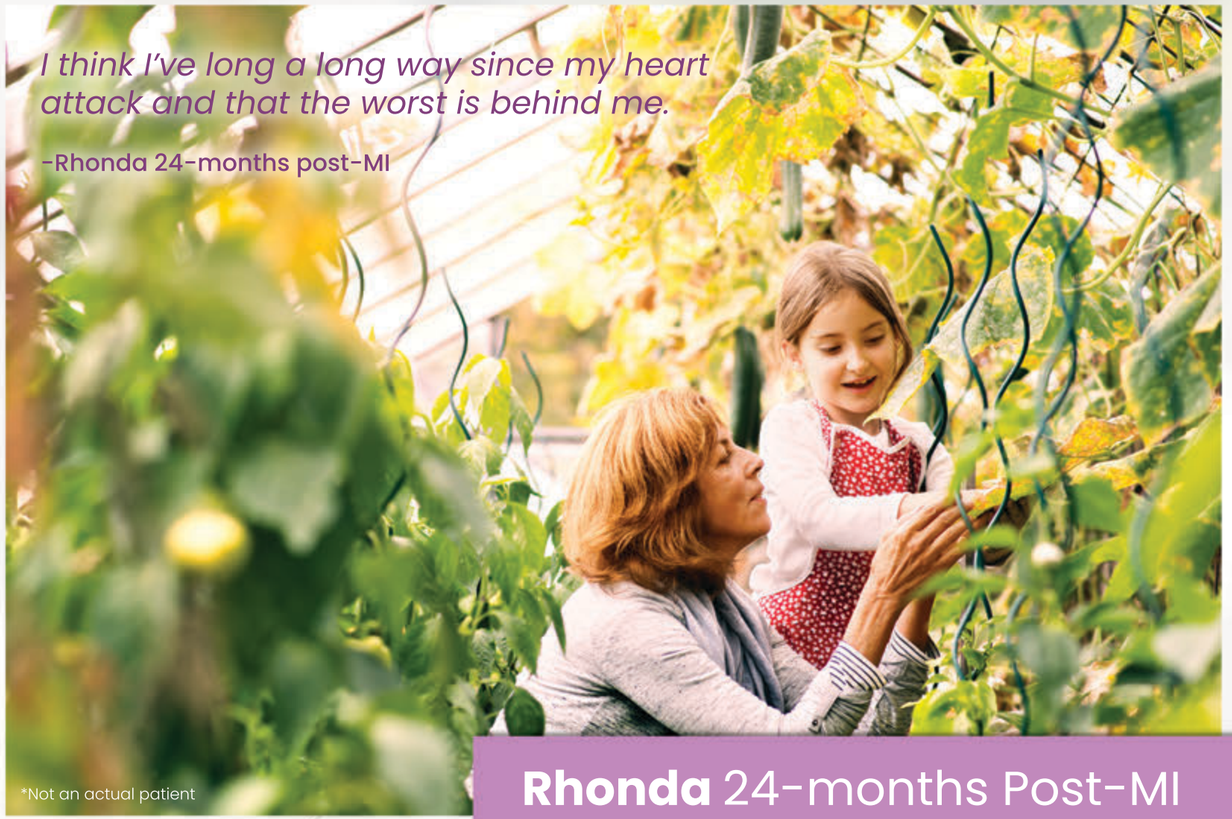
Complacent and non-compliant



*Not an actual patient

Rhonda 24-months Post-MI

- Retired accountant who spends her time gardening with her grandchildren
- Has been focused on her health ever since suffering a heart attack 2 years ago
- Now feels like she can afford to take a break from her aspirin regimen until stomach discomfort subsides

Is your patient underestimating the impact of discontinuing aspirin **because of GI symptoms?**

Age: 62 Sex: Female Body Mass Index: 28 kg/m^2

Ethnicity: Caucasian

Medical History:
MI 2 years ago
Chronic heartburn caused by GERD

Medication Regimen:
Statin, Aspirin

Coverage: Commerical

Notes: *Complains of stomach discomfort; recently stopped taking aspirin*

If your patients are at risk for discontinuing aspirin treatment due to GI symptoms, talk to them about Yosprala®

GERD. gastroesophageal reflux disease, **GI**. gastrointestinal, **MI**. myocardial infarction.

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Important Safety Information

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
- Patients with known hypersensitivity to aspirin, omeprazole, substituted benzimidazoles, or to any of the excipients in the formulation
- Proton pump inhibitor (PPI)–containing products, including Yosprala, are contraindicated in patients receiving rilpivirine-containing products

Warnings and Precautions

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.

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. 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.

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.

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.

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.

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.

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 adult patients who experience gastric symptoms during treatment with Yosprala or have a symptomatic relapse after completing treatment. In older patients, also consider an endoscopy.

Acute Interstitial Nephritis
Acute interstitial nephritis has been observed in patients taking PPIs including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue Yosprala if acute interstitial nephritis develops.

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, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Use the lowest dose and shortest duration of Yosprala™ appropriate to the condition being treated.

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.

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. 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.

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. Systemic exposure to omeprazole is increased in patients with hepatic impairment. Avoid Yosprala in patients with any degree of hepatic impairment.

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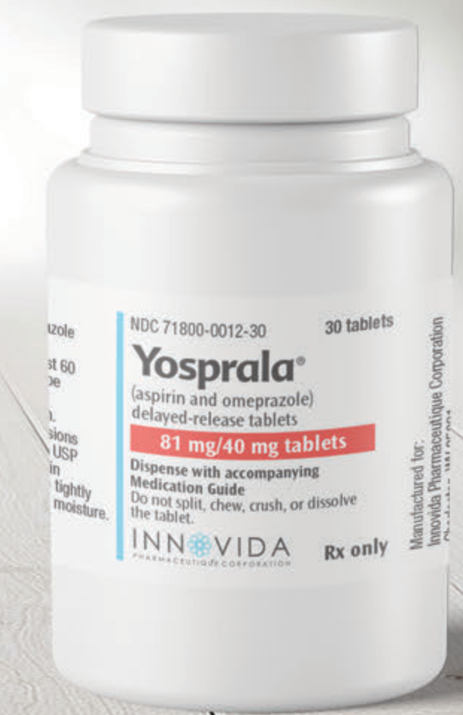

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