delayed-release tablets

Yosprala™

(aspirin and omeprazole)

THE PROTECTION IS MUTUAL

Yosprala™—the only therapy designed to sequentially deliver immediate-release omeprazole and delayed-release aspirin (ASA) for patients who require ASA for secondary prevention of cardiovascular and cerebrovascular events and are at risk for developing ASA-associated gastric ulcers[1]

Please see full Indications and Usage and additional Important Safety Information on pages 9-11.
Please see accompanying full Prescribing Information.

For more information
1-888-202-0649
yosprala@innovida.com

INNOVIDA
PHARMACEUTIQUE CORPORATION

Visit our websites
www.yospralahcp.com
www.innovidarx.com

delayed-release tablets
Yosprala™
(aspirin and omeprazole)

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.

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

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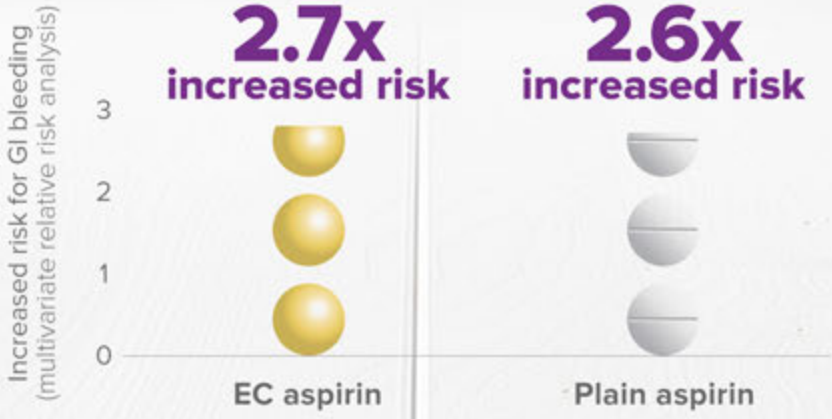
For secondary prevention of CV events,

DAILY ASPIRIN REMAINS A GOLD STANDARD, BUT CAN LEAD TO GI AEs

Daily aspirin is important for secondary prevention of CV events
- Known since 1950 to provide beneficial antiplatelet properties, which have been affirmed in multiple clinical studies[2-4]
- Recommended for secondary prevention by several US clinical practice guidelines[5-7]

Enteric-coated (EC) aspirin shows little benefit of reducing the risk of GI bleeding vs plain aspirin

EC and plain aspirin (≤325 mg/day) have a comparable risk for GI bleeding[8]



Even low-dose regimens can cause GI AEs[9]
- **2.6x** increased risk of upper GI bleeding (≤100 mg/day) vs no aspirin[9]

GI AEs can increase the risk of aspirin discontinuation[10,*]
- **1.7x** increased risk with dyspepsia or gastritis
- **1.8x** increased risk with esophageal ulcer
- **5.5x** increased risk with peptic ulcer

AE, adverse event, **CV**, cardiovascular, **GI**, gastrointestinal.

*Based on odds ratio calculation of aspirin discontinuation vs non-discontinuation.[10]

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ASPIRIN DISCONTINUATION LEADS TO INCREASED CV RISK

A rapid and significant risk of CV event recurrence or death has been associated with aspirin discontinuation[11,12]

Aspirin discontinuation due to a GI bleed increases CV risk[12]

nearly
7-fold increased risk for CV event† or death (95% CI, 1.3-35.4)

- 3x higher risk of MACE (P=0.0001) within an average of 11 days of aspirin discontinuation in patients with CAD (95% CI, 10.25-11.07)[11]

†CV event defined as acute MI, ischemic stroke, or transitory ischemic attack occurring after hospital discharge.[12]

Guidelines recommend GI risk assessment and PPI co-prescription for patients with[13]:

- History of ulcer
- Aged ≥60 years
- Dual antiplatelet and/or concomitant anticoagulant therapies during aspirin use

CAD, coronary artery disease, **MACE**, major adverse cardiac event, **MI**, myocardial infarction, **PPI**, proton pump inhibitor.

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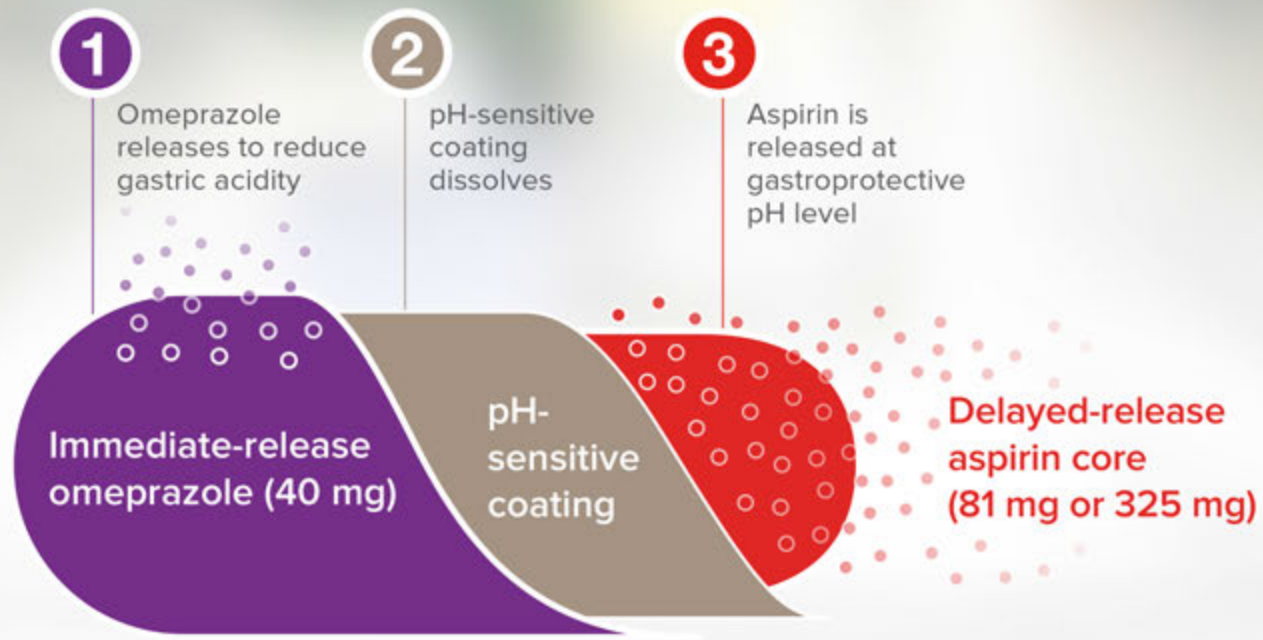
COORDINATED OMEPRAZOLE AND ASPIRIN DELIVERY

Yosprala proprietary Intelli-COAT™ system is designed to sequentially deliver immediate-release omeprazole and delayed-release aspirin[1,14]



For illustration purposes only. Not a visual representation of the tablet.

- Yosprala is not interchangeable with the individual components of aspirin and omeprazole[1]

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.

Please see Indications and Usage and additional Important Safety Information on pages 9-11.
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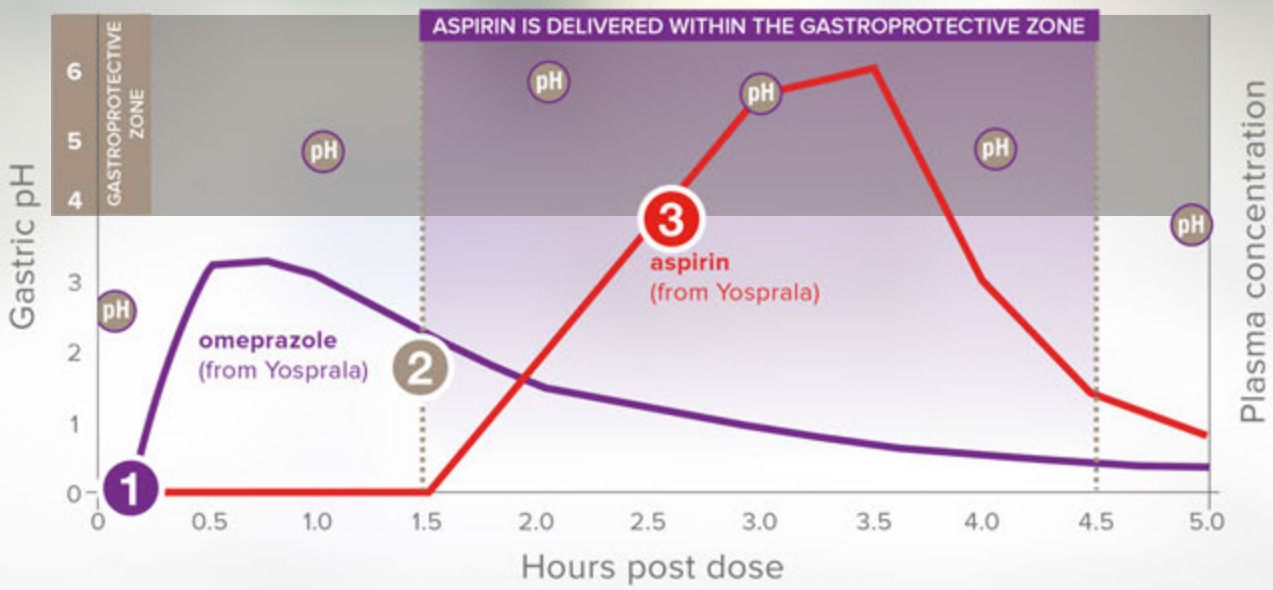
ASPIRIN DELIVERED IN THE GASTROPROTECTIVE pH ZONE

Aspirin is delivered after gastric pH has been elevated[14,*]

Yosprala™ hourly median gastric pH and PK profile over 5 hours on day 7[15,16]



- pH-sensitive coating dissolves at pH >5.514[14]

PK, pharmacokinetics.
*With Yosprala, mean percent time gastric pH >4 over 24 hours was 51%[1,15]

Warnings and Precautions

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.

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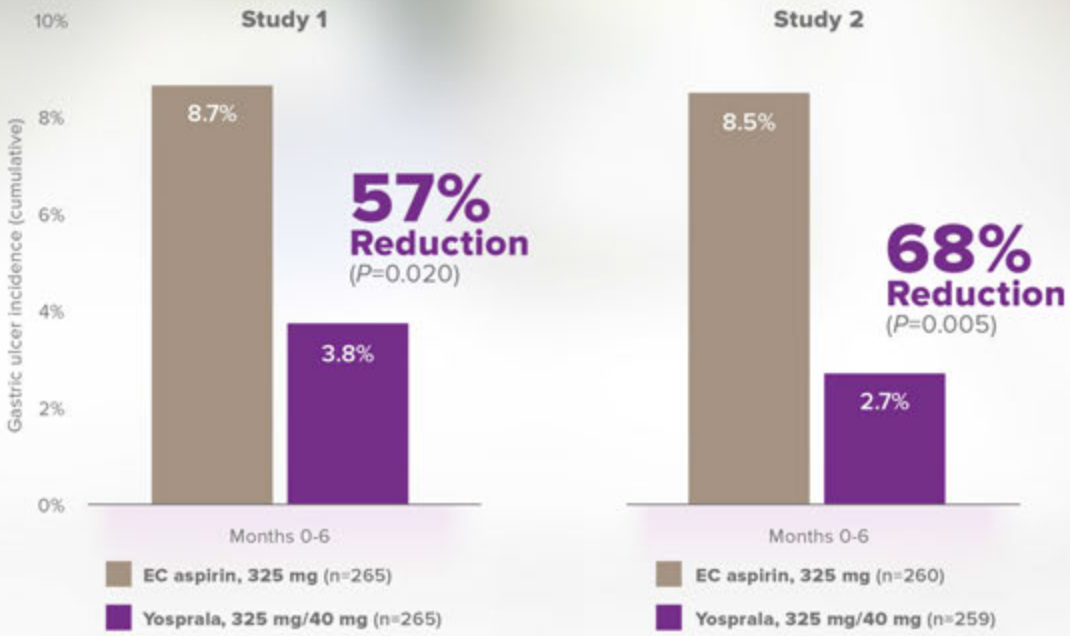
For patients requiring aspirin for secondary prevention of cardiovascular and cerebrovascular events,

HELP PROTECT PATIENTS FROM ASPIRIN-ASSOCIATED GASTRIC ULCERS

>50% fewer endoscopic gastric ulcers with Yosprala™ vs EC aspirin in 2 identically designed studies in aspirin-tolerant patients[1,17]

Primary endpoint: reduction in endoscopic gastric ulcers at 6 months[1]



- After 1 month of treatment and at all study time points, patients had fewer gastric ulcers with Yosprala vs EC aspirin[1,17-19]

71% fewer gastric and/or duodenal ulcers with Yosprala vs EC aspirin (3.4% vs 11.6% [P<0.001])[1,17]

Study design: Efficacy of the omeprazole component in Yosprala was evaluated in 2 randomized, multicenter, double-blind, 6-month, Phase 3 trials in patients who had a cerebrovascular or CV diagnosis and were taking 325 mg of aspirin for ≥3 months, expected to continue treatment for ≥6 months, and at risk for aspirin-associated gastric ulcers based on being ≥55 years-of-age or 18 to 54 years old with a documented history of gastric or duodenal ulcer within the 5 years before study enrollment. Patients received Yosprala 325-mg delayed-release aspirin/40-mg immediate-release omeprazole or 325-mg of entericcoated aspirin. Gastric and duodenal ulcer formation was assessed by gastroduodenal endoscopy at screening and after 1, 3, and 6 months of treatment.[1,17-19]

Important Safety Information

Warnings and Precautions

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.

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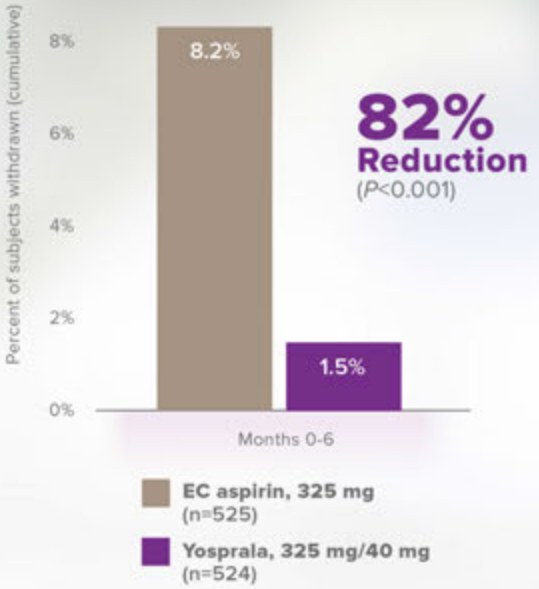
HELP REDUCE ASPIRIN DISCONTINUATIONS DUE TO GI AEs

82% fewer patients treated with Yosprala™ discontinued therapy due to pre-specified upper GI AEs vs EC aspirin[17]

Rate of discontinuation due to pre-specified upper GI AEs at 6 months[17]



Warnings and Precautions

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 osteoporosisrelated 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.

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YOSPRALA™ SAFETY PROFILE

Adverse reactions (ARs) that occurred in ≥2% of patients in the Yosprala arm and were more common than in the control arm[1]

	EC aspirin, 325 mg (n=524)	**Yosprala, 325 mg/40 mg (n=521)**
Gastritis	16%	**18%**
Nausea	2%	**3%**
Diarrhea	2%	**3%**
Gastric polyps	1%	**2%**
Noncardiac chest pain	1%	**2%**

- 7% discontinuation rate due to ARs with Yosprala (vs 11% with EC aspirin)[1]
- Less common ARs in Yosprala-treated patients included: 2 patients with upper GI bleeding (gastric or duodenal), 2 patients with lower GI bleeding (hematochezia and large intestinal hemorrhage), and 1 patient with obstruction in the small bowel[1]

For a more comprehensive list of adverse events for aspirin or omeprazole, please refer to the Warnings of their respective Prescribing Information.

Important Safety Information

Warnings and Precautions

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.

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.

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SIMPLE DOSING

Prescription-strength omeprazole with 2 aspirin strengths[1]

• 1 daily tablet, administered at least 1 hour before a meal[1,*]

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

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

*The tablets are to be swallowed whole with liquid. Do not split, chew, crush, or dissolve the tablet.[1]
For illustration purposes only. Not a visual representation of the tablets.

Programs are available to help your eligible patients save on their Yosprala™ prescription†

†Certain restrictions apply.

Warnings and Precautions

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).

Abnormal Laboratory Tests
Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

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.

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- 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
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Gastrointestinal Adverse Reactions
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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.

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Renal Failure
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Clostridium difficile-Associated Diarrhea
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Bone Fracture
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Hepatic Impairment
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Cyanocobalamin (Vitamin B12) Deficiency
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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
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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).

Please see Indications and Usage and additional Important Safety Information on page 11.

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Important Safety Information

Abnormal Laboratory Tests
Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

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.

Please see Indications and Usage and additional Important Safety Information on pages 9-10.

Please see accompanying full Prescribing Information.

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For patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and are at risk for aspirin-associated gastric ulcers[1]

delayed-release tablets
Yosprala™
(aspirin and omeprazole)

OFFER YOUR PATIENTS MUTUAL PROTECTION WITH YOSPRALA™

CV and GI protection with the only immediate-release omeprazole and delayed-release aspirin therapy[1]

- **GI AEs can increase the risk of aspirin discontinuation**, which increases CV risk[10-12]
- **Yosprala sequentially delivers immediate-release omeprazole and delayed-release aspirin** for gastro- and cardioprotection[14]
- **>50% fewer endoscopic gastric ulcers with Yosprala** vs EC aspirin over 6 months[1]
- **82% fewer patients treated with Yosprala discontinued aspirin therapy** due to pre-specified upper GI AEs vs EC aspirin[17]
- **ARs that occurred in ≥2% of patients** in the Yosprala arm and were more common than in the control arm: gastritis (18% vs 16%), nausea (3% vs 2%), diarrhea (3% vs 2%), gastric polyps (2% vs 1%), noncardiac chest pain (2% vs 1%)[1]
- 1 tablet, once daily, at least 1 hour before a meal[1]

For more information, please visit **yospralahcp.com**

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Important Safety Information

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

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

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