YOSPRALA™ (aspirin and omeprazole) oral delayed release tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Description:

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; for reducing the combined risk of death and nonfatal myocardial infarction (MI) in patients with a previous MI or unstable angina pectoris; for reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris; for 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. Yosprala is not indicated for use as the initial dose of aspirin therapy during onset of acute coronary syndrome, acute MI or before percutaneous coronary intervention.
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.

Yosprala has not been shown to reduce the risk of gastrointestinal (GI) bleeding due to aspirin. Risk factors for GI bleeding with aspirin use include history of ulcer complication, history or ulcer disease (non-bleeding), GI bleeding, dual antiplatelet therapy, concomitant anticoagulant therapy, age ≥ 60 years, corticosteroid use, and dyspepsia or gastrointestinal reflux symptoms. Other risk factors associated GI bleeding include higher aspirin dose and longer duration of use, bleeding disorders, renal failure, severe liver disease, and thrombocytopenia. Due to these risk factors for GI complications, gastroprotective therapy is recommended. PPIs such as lansoprazole, omeprazole, pantoprazole, rabeprazole, and others are preferred for the treatment and prevention of aspirin associated GI complications.

Aspirin (acetylsalicylic acid) is an inhibitor of both prostaglandin synthesis and platelet aggregation. Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A2. At higher doses, aspirin reversibly inhibits the formation of prostaglandin I2 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

Omeprazole belongs to a class of anti-secretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the [H /K]-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor (proton pump inhibitor), in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion regardless of the stimulus.

Yosprala is a multilayered film coated, delayed release tablet of an enteric coated delayed release aspirin core surrounded by an immediate release omeprazole layer. Enteric coated products are irregularly absorbed from the gastrointestinal tract. Omeprazole stability is a function of gastric pH; it is rapidly degraded in an acidic environment but it is stable under alkaline conditions. With the Yosparla formulation, the immediate release omeprazole component is embedded within a film coat where it is available for instantaneous dissolution, while aspirin release occurs only after reaching a GI tract pH > 5.5.

Yosprala is available in either 81 mg or 325 mg aspirin with 40 mg omeprazole tablet strengths.

Definitions:

Drug related events:

- Ineffective / failure
  Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be
YOSPRALA™ (aspirin and omeprazole) oral delayed release tablet (cont.)

documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.
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Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Yosprala (aspirin and omeprazole) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- Initial therapy: FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Yosprala (aspirin and omeprazole) is considered medically necessary when ALL of the following criteria are met:

1. Individual is 18 years of age or older

2. Medical record documentation of a confirmed diagnosis of ALL of the following:
   - Individual requires aspirin for secondary prevention of cardiovascular or cerebrovascular events that includes ONE of the following:
     - Nonfatal stroke in an individual who had an ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli
     - Nonfatal MI in an individual with a previous MI or unstable angina pectoris
     - Individual with chronic stable angina pectoris
     - Individual has undergone revascularization procedures (CABG or PTCA) when there is a pre-existing condition for which aspirin is already indicated
   - Individual is at risk for developing aspirin associated gastric ulcers due to ONE of the following:
     - Age is 55 years or older
     - Documented history of gastric ulcer

3. Medical record documentation that the individual is unable to use ALL of the following due to failure or adverse drug event:
   - Simultaneous use of enteric coated aspirin 81 mg with ALL preferred PPIs: Dexilant (dextansoprazole) 60 mg, esomeprazole magnesium 40 mg, lansoprazole 30 mg, omeprazole 40 mg, pantoprazole 40 mg, and rabeprazole 20 mg
   - Simultaneous use of enteric coated aspirin 325 mg with ALL preferred PPIs: Dexilant (dextansoprazole) 60 mg, esomeprazole magnesium 40 mg, lansoprazole 30 mg, omeprazole 40 mg, pantoprazole 40 mg, and rabeprazole 20 mg

4. Absence of ALL of the following contraindications:
YOSPRALA™ (aspirin and omeprazole) oral delayed release tablet (cont.)

- History of asthma, urticarial, or other allergic type reactions after taking aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs)
- Known hypersensitivity to aspirin, omeprazole, substituted benzimidazoles or to any of the excipients of Yosprala
- Individuals receiving rilpivirine containing products (such as Complera®, Endurant®, Odefsey®)
- Pediatric individual with suspected viral infection (with or without a fever)

5. Absence of ALL of the following exclusions:
   - Simultaneous use of Yosprala 325/40 mg strength with Brilinta (ticagrelor)
   - Simultaneous use with clopidogrel
   - Simultaneous use with St. John’s wort or rifampin
   - Simultaneous use with atazanavir containing products (such as Evotaz™, Reyataz®) or nelfinavir (such as Viracept®)
   - Simultaneous use with Vfend® (voriconazole)
   - Severe renal failure (glomerular filtration rate of < 10 mL/min)
   - All degrees of hepatic impairment
   - Active or clinically significant bleeding from any source
   - Individual with interstitial nephritis
   - Individual with cutaneous lupus erythematosus or systemic lupus erythematosus
   - Third trimester of pregnancy (30 weeks or more of gestation)
   - Woman who is breast feeding an infant or child

- **Continuation of coverage (renewal request):** Yosprala (aspirin and omeprazole) is considered *medically necessary* with documentation of ALL of the following:
  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- **Yosprala (aspirin and omeprazole)** for all other indications not previously listed is considered *experimental or investigational* based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Initial dose of aspirin therapy during onset of acute coronary syndrome (ACS)
- Initial dose of aspirin therapy during acute myocardial infarction (MI)
- Initial dose of aspirin therapy before percutaneous coronary intervention (PCI)

FDA-approved indication and dosage:

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<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tr>
<td>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.</td>
<td>One tablet daily at least 60 minutes before a meal. Do not split, chew, crush or dissolve the tablet.</td>
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