Drug Monograph

Drug/Drug Class:	**Yosprala® (aspirin and omeprazole) film coated tablet/ Proton Pump Inhibitors**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Yosprala® is available in a film coated tablet containing 81 mg aspirin with 40 mg omeprazole or 325 mg aspirin with 40 mg omeprazole. Manufacturer: Aralez Pharmaceuticals US Inc., Princeton, NJ 08540
Summary of Findings:	In a pooled analysis of 2 randomized studies of patients with established cardiovascular or cerebrovascular disease who were at risk for gastric ulcers associated with aspirin use (N=1049), endoscopic gastric ulcers occurred significantly less often with Yosprala® 325 mg/40 mg compared with EC Aspirin 325 mg alone (6-month event rate, 3.2% vs 8.6%).
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [3]

Aspirin has long been used in patients to prevent second heart attacks and strokes, but it increases the risk of stomach problems, including gastric ulcers. Gastrointestinal symptoms are often cited as the reason patients discontinue therapy. The omeprazole component has been added to help reduce that risk.

Dosage Form(s) [1]

Yosprala® is available in a film coated tablet containing 81 mg aspirin with 40 mg omeprazole or 325 mg aspirin with 40 mg omeprazole.

Manufacturer [1]

Aralez Pharmaceuticals US Inc., Princeton, NJ 08540

Indication(s) [1]

Yosprala® is indicated for secondary prevention of cardiovascular and cerebrovascular events in adults who require aspirin, but who are at risk of developing gastric ulcers associated with aspirin.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Aspirin inhibits platelet aggregation by irreversibly inhibiting prostaglandin cyclooxygenase, which prevents the formation of thromboxane A2. At higher doses, it also reversibly inhibits the formation of prostacyclin, an arterial vasodilator. Omeprazole suppresses gastric acid secretion by inhibiting the proton pump within the gastric mucosa, thereby blocking the final step of acid production.

Pharmacokinetics:

	Aspirin	**Omeprazole**
Protein Binding	75% to 90%	95%
Metabolism	Plasma via hydrolysis; liver via conjugation	Hepatic via CYP2C19 (major) and CYP3A4 to inactive metabolites
Excretion	Urine, 5% to 80%	Urine, 77% (metabolites) Feces, 23%
Half-life	Aspirin, 0.35 hour; salicylic acid, 2.4 hours	1 hour

Prevention of Gastric Ulcers

Treatment with Yosprala® resulted in fewer gastric ulcers than EC Aspirin alone when used as secondary prevention of cardiovascular and cerebrovascular events.

STUDY DESIGN	Pooled analysis of 2 randomized, double-blind studies (N=1049)
INCLUSION CRITERIA	Adults with established cardiovascular or cerebrovascular disease who were taking aspiring 325 mg daily and were at risk for gastric ulcers associated with aspirin use.
EXCLUSION CRITERIA	Upper GI ulcer, positive H pylori test, or recent coronary revascularization.
TREATMENT REGIMEN	Patients were randomized to Yosprala® 325 mg/40 mg or EC aspirin 325 mg orally once daily for up to 6 months.
RESULTS	Patients on Yosprala® 325 mg/40 mg experienced a 6 month event rate of endoscopic gastric ulcers of 3.2% vs an 8.6% 6 month event rate for those patients taking EC Aspirin 325 mg alone. Discontinuation due to upper GI adverse events was also significantly less (1.5% vs 8.2%).
SAFETY	The rate of major adverse cardiovascular events was similar between groups.

Contraindications (1)

- History of asthma, rhinitis, and nasal polyps syndrome, or other allergic reaction to aspirin or other NSAIDs
- Hypersensitivity to aspirin, omeprazole, substituted benzimidazoles, or any excipient of the product
- Pediatric patients with suspected viral infection, with or without fever; may increase risk of Reye's syndrome
- Concomitant use of rilpivirine-containing products

Warnings and Precautions (1)

- Use may increase bleeding time; increased risk in patients with inherited or acquired bleeding disorders; monitoring recommended.
- Severe gastrointestinal (GI) reactions including inflammation, bleeding ulceration, intestinal hemorrhage, small bowel obstruction, and perforation of the upper and lower GI tract may occur with use, even in the absence of GI symptoms; monitoring recommended and discontinue use for active and clinically significant bleeding.
- GI symptoms (eg, dyspepsia, stomach pain, heartburn, nausea, vomiting) have been reported.
- Avoid concomitant use of clopidogrel.

- Avoid concomitant use of ticagrelor with the aspirin 325 mg/omeprazole 40 mg dose; maintenance doses of aspirin above 100 mg may reduce ticagrelor efficacy.
- Avoid concomitant use of St. John's Wort or rifampin.
- Avoid use in severe renal failure (GFR less than 10 mL/min).
- Aspirin has been associated with elevated BUN, serum creatinine, hyperkalemia, proteinuria, and an increased risk of chronic renal failure.
- Acute interstitial nephritis has been reported with proton pump inhibitor use and may occur at any time during therapy; discontinuation required.
- Symptomatic response does not preclude the presence of GI malignancy; monitor patients with persistent symptoms or symptomatic relapse despite therapy.
- Clostridium difficile-associated diarrhea (CDAD) may occur with proton pump inhibitor use, particularly in hospitalized patients; monitoring recommended if diarrhea occurs and use lowest dose and shortest treatment duration as appropriate.
- Proton pump inhibitor use may increase risk of osteoporosis-related bone fractures of the hip, wrist, or spine, particularly with high-doses or long term use; use lowest dose and shortest treatment duration as appropriate.
- New onset or exacerbations of cutaneous lupus erythematosus and systemic lupus erythematosus have been reported with proton pump inhibitor use, with an increased risk in older patients; avoid use for longer than indicated and discontinue use if signs or symptoms develop.
- Elevations in serum ALT levels may occur with prolonged moderate to high doses of aspirin, with or without mild bilirubin elevations; discontinue if occurs.
- Avoid use in any degree of hepatic impairment.
- Cyanocobalamin (vitamin B12) deficiency may occur with prolonged acid suppression (eg greater than 3 years).
- Hypomagnesemia has been reported in patients treated with proton pump inhibitors for at least 3 months and may lead to serious adverse effects (eg, tetany, arrhythmias, and seizures); increased risk after a year of therapy; monitor if prolonged use is expected or with concomitant digoxin or other drugs that cause hypomagnesemia.
- Increased risk of false-positive serum chromogranin A results for the diagnosis of neuroendocrine tumors; interrupt therapy prior to diagnostic testing.
- Increased risk of false-positive results in secretin stimulation test for the diagnosis of gastrinomas; interrupt therapy prior to diagnostic testing.
- Avoid use in the third trimester (30 weeks) of pregnancy due to potential for NSAID-associated premature closure of the fetal ductus arteriosus.
- Infertility may occur with NSAID use; consider interruption in therapy if suspected infertility occurs.
- Avoid use in patients from Asian ancestry with unknown CYP2C19 genotype or those known to be poor metabolizers.

Adverse Effects [1]

Most common, ≥ 2%	Yosprala® (n=521)	EC Aspirin (n=524)
Gastritis	18%	16%
Nausea	3%	2%
Diarrhea	3%	2%
Gastric polyps	2%	1%
Non-cardiac chest pain	2%	1%

Drug Interactions [1]

- Acetazolamide
- Antihypertensives: ACE inhibitors, beta blockers, diuretics
- Antiretrovirals: Saquinavir, rilpivirine, atazanavir, nelfinavir
- CYP2C19 substrates: Clopidogrel, citalopram, cilostazol, phenytoin, diazepam
- CYP2C19 or CYP3A4 inducers, strong: Rifampin, St. John's Wort, ritonavir
- CYP2C19 or CYP3A4 inhibitors: Voriconazole
- Digoxin
- Disulfiram
- Gastric pH-dependent drugs: Iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole, itraconazole
- Heparin
- Immunosuppressants: Cyclosporine, tacrolimus
- Methotrexate
- NSAIDs
- Oral hypoglycemics
- Ticagrelor
- Uricosuric agents: Probenecid
- Valproic acid
- Warfarin

Dosage and Administration [1]

The FDA recommended dose is Aspirin 81 mg/ Omeprazole 40 mg orally once daily, taken at least 60 minutes before a meal. Aspirin 325 mg/Omeprazole 40 mg once daily may be considered. Use lowest effective dose to achieve treatment goals and avoid dose-dependent adverse effects.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Aspirin/ Omeprazole Delayed-Release	Yosprala	Aralaex	81 mg/40 mg tablets	1 tablet daily	$150*
			325 mg/40 mg tablets	1 tablet daily	$150*
Aspirin	Generic	Marlex	81 mg EC tablets	1 tablet daily	$0.30**
			325 mg EC tablets	1 tablet daily	$0.30**
Omeprazole Delayed-Release	Prilosec	AstraZeneca	40 mg capsule	1 capsule daily	$3.30**

*Wholesale Acquisition Cost

** Maximum Allowable Cost

Conclusion

Yosprala® is indicated in adults who require aspirin for secondary prevention of cardiovascular and cerebrovascular events, but who are risk of developing gastric ulcers associated with aspirin use. The combination of aspirin-omeprazole tablet contains an inncer core of EC aspirin surrounded by an outer layer of immediate-release omeprazole. The outer omeprazole layer is immediately released to raise the gastric PH level. The aspirin core is then released only after the gastric PH rises above 5.5. Yosprala® may have an advantage in improving compliance, but will come at a cost. Its cost is over $140 more expensive per month than taking each ingredient individually. Yosprala® has exhibited superior results to EC Aspirin 325 mg alone in pooled analysis; however, studies have not been conducted with a combination of EC Aspirin with omeprazole delayed-release formulations. It is not for use during onset of acute coronary syndrome or acute myocardial infarction, or for use prior to percutaneous coronary intervention, where immediate-release aspirin is appropriate.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1) Product Information: Yosprala™, aspirin/omeprazole delayed-release tablets. Aralez Pharmaceuticals US Inc, Princeton, NJ, 09/2016.
2) Whellan DJ, Goldstein JL, Cryer BL et al: PA32540 (a coordinated-delivery tablet of enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) versus enteric-coated aspirin 325 mg alone in subjects at risk for aspirin-associated gastric ulcers: results of two 6-month, phase 3 studies. AM Heart J 2014; 68(4): 495-502.
3) Liu, Angus. Aralez finally scores FDA approval for Yosprala, but the combo med could be a hard sell. Retrieved 5/22/17 from: http://www.fiercepharma.com/drug-delivery/fda-approves-aspirin-and-omeprazole-combo-drug-yosprala

Prepared by: Luke Boehmer PharmD

Date: May 22, 2017