Proton Pump Inhibitors (PPIs) Step Therapy and Quantity Limit Program Summary

For the **Medicaid** formularies, step therapy will target Nexium suspension packets. Any generic PPI except omeprazole/sodium bicarbonate can serve as a prerequisite. For groups with the OTC benefit, omeprazole OTC and Prilosec OTC will also qualify as prerequisites.

For the **GenRx Closed** formulary, step therapy will target Nexium suspension packets. Any generic PPI except omeprazole/sodium bicarbonate can serve as a prerequisite. For groups with the OTC benefit, omeprazole OTC and Prilosec OTC will also qualify as prerequisites.

For the **GenRx Open, Health Insurance Marketplace & KeyRx** formularies, step therapy will target ALL brand PPIs and generic omeprazole/sodium bicarbonate. Any generic PPI except omeprazole/sodium bicarbonate can serve as a prerequisite. For groups with the OTC benefit, omeprazole OTC and Prilosec OTC will also qualify as prerequisites.

For the **FlexRx Closed** formulary, step therapy will target Nexium suspension packets. Any generic PPI except omeprazole/sodium bicarbonate can serve as a prerequisite. For groups with the OTC benefit, omeprazole OTC and Prilosec OTC will also qualify as prerequisites.

For the **FlexRx Open** formulary, step therapy will target ALL brand PPIs and generic omeprazole/sodium bicarbonate. Any generic PPI except omeprazole/sodium bicarbonate can serve as a prerequisite. For groups with the OTC benefit, omeprazole OTC and Prilosec OTC will also qualify as prerequisites.

This program is a GenRx Standard and FlexRx Standard Step Therapy Program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

FDA APPROVED INDICATIONS AND DOSAGE[1-7,10,17]

AGENTS	INDICATION	DOSAGE AND ADMINISTRATION
Aciphex (raberprazole) tablet[a]	Healing of erosive or ulcerative Gastroesophageal Reflux Disease (GERD)	20 mg once daily for four to eight weeks. For those who have not healed after eight weeks, an additional eight week course may be considered.
	Maintenance of healing of erosive or ulcerative Gastroesophageal Reflux Disease (GERD)	20 mg once daily.

AGENTS	INDICATION	DOSAGE AND ADMINISTRATION
	Treatment of symptomatic Gastroesophageal Reflux Disease (GERD)	For Adults: 20 mg once daily for four weeks. If symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered. For adolescents 12 years of age or older: 20 mg once daily for up to 8 weeks.
	Healing of duodenal ulcers	20 mg once daily for up to four weeks. A few patients may require additional therapy to achieve healing.
	Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence	20 mg twice daily for seven days.
	Treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome	60 mg once daily. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients may require divided doses.
Aciphex Sprinkle (rabeprazole) delayed release capsule	Treatment of Gastroesophageal Reflux Disease (GERD) in pediatric patients 1 to 11 years of age	<15 kg: 5-10 mg once daily for up to 12 weeks ≥15 kg: 10 mg once daily for up to 12 weeks
Dexilant (dexlansoprazole) capsule	Healing of all grades of erosive esophagitis in patients 12 years of age and older	60 mg once daily for up to 8 weeks
	Maintenance of healed EE and relief of heartburn in patients 12 years of age and older	30 mg once daily Controlled studies did not extend beyond 6 months in adults and 16 weeks in patients 12 to 17 years of age
	Treatment of symptomatic non-erosive gastroesophageal reflux disease (GERD) in patients 12 years of age and older	30 mg once daily for 4 weeks

AGENTS	INDICATION	DOSAGE AND ADMINISTRATION
Dexilant Solutab (dexlansoprazole) oral disintegrating tablet	Maintenance of healed EE and relief of heartburn in patients 12 years of age and older	30 mg once daily Controlled studies did not extend beyond 6 months in adults and 16 weeks in patients 12 to 17 years of age
	Treatment of symptomatic non-erosive gastroesophageal reflux disease (GERD) in patients 12 years of age and older	30 mg once daily for 3 weeks
Esomeprazole Strontium delayed release capsule	Treatment of gastroesophageal reflux disease (GERD)	24.65 or 49.3 mg once daily for 4-8 weeks
	Risk reduction of NSAID-associated gastric ulcer	24.65 or 49.3 mg once daily for up to 6 months
	H. pylori eradication to reduce the risk of duodenal ulcer recurrence	49.3 mg once daily for 10 days
	Pathological hypersecretory conditions, including Zollinger-Ellison syndrome	49.3 mg twice daily
Nexium (esomeprazole) delayed release capsule[a], delayed release suspension packet	Treatment of gastroesophageal reflux disease (GERD)	2.5-40 mg once daily for up to 8 weeks
	Risk reduction of NSAID-associated gastric ulcer	20-40 mg once daily for up to 6 months
	H. pylori eradication to reduce the risk of duodenal ulcer recurrence	30 mg once daily for up to 10 days
	Pathological hypersecretory conditions, including Zollinger-Ellison syndrome	40 mg twice daily
Prevacid (lansoprazole) enteric coated capsule, delayed release suspension packet, delayed release capsule[a], oral disintegrating tablet[a]	Short-term treatment of active duodenal ulcer	15 mg once daily for 4 weeks
	H. pylori eradication to reduce the risk of duodenal ulcer recurrence	30 mg twice daily for 10 -14 days 30 mg three times daily for 14 days
	Maintenance of healed duodenal ulcers	15 mg once daily
	short-term treatment of active benign gastric ulcer	30 mg once daily for 8 weeks
	Healing of nonsteroidal anti-inflammatory drugs (NSAID)-associated gastric ulcer	30 mg once daily for 8 weeks
	Risk reduction of NSAID-associated gastric ulcer	15 mg once daily for 12 weeks
	Gastroesophageal Reflux Disease (GERD)	15-30 mg once daily for 8-12 weeks
	Maintenance of healing of Erosive Esophagitis (EE)	15 mg once daily
	Pathological hypersecretory conditions including Zollinger-Ellison Syndrome (ZES)	60 mg once daily

AGENTS	INDICATION	DOSAGE AND ADMINISTRATION
Prilosec (omeprazole) capsule[a], delayed release capsule[a], powder pack for suspension	Treatment of active duodenal ulcer in adults	20 mg once daily for 4 weeks Some patients may require an additional 4 weeks
	Eradication of Helicobacter pylori to reduce the risk of duodenal ulcer recurrence in adults	20 mg twice daily for 10 days as part of triple therapy; if ulcer present, continue with 20 mg once daily for an additional 18 days 40 mg once daily for 14 days as part of dual therapy; if ulcer present continue with 20 mg once daily for an additional 14 days
	Treatment of active benign gastric ulcer in adults	40 mg once daily for 4-8 weeks
	Treatment of symptomatic gastroesophageal reflux disease (GERD) in patients 1 year of age and older	5-20 mg once daily for up to 4 weeks
	Treatment of erosive esophagitis (EE) due to acid-mediated GERD in patients 1 month of age and older	1 month to <1 year of age: • 2.5-10 mg once daily for up to 6 weeks ≥1 year of age: • 5-20 mg once daily for 4-8 weeks
	Maintenance of healing of EE due to acid-mediated GERD in patients 1 year of age and older	5-20 mg once daily
	Pathologic hypersecretory conditions in adults	60 mg once daily to 120 mg three times daily
Protonix (pantoprazole) enteric coated tablet[a], delayed release suspension packet	Short-term treatment of erosive esophagitis associated with Gastroesophageal Reflux Disease (GERD)	20-40 mg once daily for up to 8 weeks
	Maintenance of healing of erosive esophagitis	40 mg once daily
	pathological hypersecretory conditions including Zollinger-Ellison Syndrome	40 mg twice daily
Zegerid (omeprazole/sodium bicarbonate) capsule[a], powder pack for suspension[a]	Short-term treatment of active duodenal ulcer	20 mg once daily for 4 weeks Some patients may require an additional 4 weeks of therapy
	Short-term treatment of active benign gastric ulcer	40 mg once daily for 4-8 weeks
	Treatment of gastroesophageal reflux disease (GERD)	20 once daily for 4-8 weeks
	Maintenance of healing of erosive esophagitis	20 mg once daily

AGENTS	INDICATION	DOSAGE AND ADMINISTRATION
	Reduction of risk of upper GI bleeding in critically ill patients	40 mg oral suspension initially followed by 40 mg 6-8 hours later and 40 mg daily thereafter for 14 days

a – generic available

CLINICAL RATIONALE

Current guidelines recognize the proton pump inhibitors (PPIs) as first-line therapy for the management of dyspepsia, gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), eradication of Helicobacter pylori (H. pylori), and Zollinger Ellison syndrome (ZES).[8,9,11-16]

In studies comparing PPIs to one another, while some differences have been reported, the magnitude of differences (safety/efficacy) has been small and of uncertain clinical importance. The degree to which any differences would justify the selection of one vs. another PPI, particularly when considering cost-effectiveness, is unclear. Data suggests the similar efficacy of PPIs that has been observed in controlled clinical trials may not necessarily translate into equivalent effectiveness when these drugs are substituted for one another.[16] Differences in dosage formulations and drug interactions may occasionally influence choice of PPI in individual cases.[8,11-13]

Safety

Aciphex is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

Dexilant is contraindicated in the following:
- Patients with known hypersensitivity to any component of the formulation.
- Patients receiving rilpivirine-containing products.

Esomeprazole Strontium is contraindicated in patients with known hypersensitivity to proton pump inhibitors (PPIs) (angioedema and anaphylaxis have occurred).

Nexium is contraindicated in patients with known hypersensitivity to proton pump inhibitors (PPIs) (angioedema and anaphylaxis have occurred).

Prevacid is contraindicated in patients with known severe hypersensitivity to any component of the formulation.

Prilosec is contraindicated in the following:
- Patients with known hypersensitivity to substituted benzimidazoles or any component of the formulation.
- Patients receiving rilpivirine-containing products.

Protonix is contraindicated in those with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

Zegerid is contraindicated in those with known hypersensitivity to any components of the formulation.

Prevacid is contraindicated in patients with known severe hypersensitivity to any component of the Prevacid formulation.

For additional clinical information see Prime Therapeutics Formulary Chapter 7.4C Proton Pump Inhibitors.

REFERENCES

1. Dexilant prescribing information. Takeda Pharmaceuticals America, Inc. October 2016.
2. Prevacid prescribing information. Takeda Pharmaceuticals, Inc. October 2016.
3. Nexium prescribing information. AstraZeneca LP. December 2016.
4. Prilosec prescribing information. AstraZeneca LP. December 2016.
5. Protonix prescribing information. Wyeth Pharmaceuticals Inc. October 2016.
6. Aciphex prescribing information. Eisai Co, Ltd. April 2016.
7. Zegerid prescribing information. Santarus, Inc. October 2016.
8. Katz PO, Gerson LB, Vela MF, et al. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013;108:308-328.
9. Drugs for peptic ulcer disease and GERD. Medical Letter Treatment Guidelines. 2014;12(140):25-30. North Am Soc for Pediatric Gastroenterology, Hepatology, & Nutrition/European Society for Pediatric Gastroenterology, Hepatology, & Nutrition Guideline H.Pylori 2011. *JPGN.* 2011;53:230-243.
10. Esomeprazole Strontium prescribing information. Amneal Pharmaceuticals/Hanmi Pharm. Co. October 2016.
11. Management of patients with ulcer bleeding. American Journal of Gastroenterology. 2012 Mar;107(3):345-60.
12. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011 Mar;140(3):1084-91.
13. Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. Expert Review Clinical Pharmacology. 2012 May;5(3):337-44.
14. The Zollinger-Ellison syndrome: dangers and consequences of interrupting antisecretory treatment. Clinical Gastroenterology and Hepatology. 2012 Feb;10(2):199-202.
15. Zollinger-Ellison syndrome: classical considerations and current controversies. The Oncologist. 2014 Jan;19(1):44-50.
16. Up to Date: Overview and comparison of PPIs for the treatment of acid-related disorders. Current through: Feb 2017. Updated: Jun 2016. Accessed 3/30/2017.
17. Aciphex Sprinkle prescribing information. FSC Laboratories, Inc. April 2016.

Proton Pump Inhibitors (PPIs) Step Therapy

OBJECTIVE
The intent of the Proton Pump Inhibitors (PPIs) Step Therapy (ST) program is to encourage the use of the cost-effective preferred generic PPIs prior to the use of brand PPIs and nonpreferred generic PPIs, and to accommodate for use of nonpreferred brand or generic PPIs when preferred generic PPIs cannot be used due to previous trial, documented intolerance, FDA labeled contraindication, or hypersensitivity. Requests for nonpreferred PPIs will be reviewed when patient-specific documentation has been provided. Only oral dosage forms of the PPIs are included in this program.

TARGET AGENTS
(all brands and *nonpreferred* generics, determined by client and benefit structure)
Aciphex® (rabeprazole)[a]
Dexilant™ (dexlansoprazole)
Esomeprazole Strontium® (brand agent)
Nexium® (esomeprazole)[a]
Prevacid® (lansoprazole)[a]
Prilosec® (omeprazole)[a]
Protonix® (pantoprazole)[a]
Zegerid® (omeprazole/sodium bicarbonate)[a]
a - available as a generic; designated target or prerequisite as determined by client

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Brand and *Nonpreferred* PPIs will be approved when ANY ONE of the following is met:
1. The patient's medication history includes use of a *preferred* prescription strength generic PPI in the past 90 days
   OR
2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity, to one of the *preferred* generic PPI prerequisites

Length of approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.

Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT
OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
    a. A statement by the prescriber that the patient is currently taking the requested agent
    AND
    b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
    AND
    c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

    OR
2. The patient's medication history include the required prerequisite/preferred agent(s) as indicated by:
    a. Evidence of a paid claim(s) within the past 999 days
    OR
    b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

    OR
3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria