Clinical Policy Title:	Proton Pump Inhibitors
Policy Number:	RxA.3
Drug(s) Applied:	rabeprazole (AcipHex®, AcipHex® Sprinkle),dexlansoprazole (Dexilant®), esomeprazole strontium (ES), esomeprazole (Nexium®, Nexium® 24HR, Nexium® 24HR ClearMinisTM), omeprazole (Prilosec® Packets),, omeprazole/sodium bicarbonate (Zegerid®, Zegerid® OTC).
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Indication	AcipHex®	Dexilant®	Nexium®	Prilosec®	Zegerid®	AcipHex® sprinkle	ES
Duodenal ulcers	X		*	X	X		
Duodenal ulcers, Maintenance				*			
Duodenal ulcers, giant				*			
Erosive esophagitis	X	X	X	X	X		X
Erosive esophagitis, Maintenance	X	X	X	X	X		X
Gastric ulcers	*			X	X		
Nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcer, risk reduction	*		X	*			X
NSAID-associated gastric ulcer, healing of			*	*			
Helicobacter pylori (*H.* pylori) Triple Therapy	X		X	X			X
H. pylori Dual Therapy				X			
H. pylori Quadruple therapy	*		*	*			

Pathological hypersecretory conditions, including Zollinger-Ellison Syndrome	X		X	X			X
Symptomatic gastroesophageal reflux disease (GERD) (erosive/ulcerative)	X		X^	X	X	X^P^	X
Symptomatic GERD, maintenance (erosive/ulcerative)	X						
Symptomatic GERD (non-erosive)		X	X				X
Indigestion	*		*	*			
Drug-induced Gastrointestinal (GI) disturbance				*			
Esophageal stricture				*			
Heartburn			X				
Reduction of risk of upper GI bleed in critically ill patients				*	X		

*Clinical trials have demonstrated the efficacy and safety for these indications, although not currently FDA-approved.

^Includes adults and pediatrics

^P^Pediatrics only

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**

rabeprazole (Aciphex®)	Duodenal ulcers; Erosive esophagitis; H. pylori triple therapy; Symptomatic GERD (erosive/ulcerative), healing and maintenance;	20 mg PO once daily (treatment duration varies)	20 mg/day
	Pathological hypersecretory conditions, including Zollinger-Ellison Syndrome	60 mg PO once daily to 60 mg PO BID	120 mg/day
rabeprazole sodium delayed-release (Aciphex® sprinkle)	Symptomatic GERD (erosive/ulcerative)	**Pediatric** Age 1 to 11 years: Weight <15 kg: 5 to 10 mg PO once daily Weight ≥15 kg: 10 mg PO once daily	10 mg/day
dexlansoprazole (Dexilant®)	Healing of erosive esophagitis	60 mg PO once daily	60 mg/day
	Maintenance of healed erosive esophagitis and relief of heartburn; Symptomatic non- erosive GERD	30 mg PO once daily	30 mg/day
esomeprazole (Nexium®, Nexium® 24HR, Nexium® 24HR clear minis)	GERD (including erosive esophagitis, symptomatic GERD)	**Adult** 20 to 40 mg PO once daily to BID **Pediatric** Age 1 to 11 years: 10 to 20 mg PO once daily; Age 12 to 17 years: 20 to 40 mg PO once daily; Age 1 month to < 1 year: Weight 3 kg to 5 kg: 2.5 mg PO once daily Weight > 5 kg to 7.5 kg: 5 mg PO once daily	80 mg/day

	Risk reduction of NSAID-associated gastric ulcer	20 mg to 40 mg PO once daily	40 mg/day
	H. pylori triple therapy	40 mg PO once daily for 10 days, in combination with amoxicillin and clarithromycin	40 mg/day
	Pathological hypersecretory conditions, including Zollinger-Ellison Syndrome	40 mg PO BID	240 mg/day
lansoprazole (Prevacid® solutab)	Duodenal ulcers	15 mg PO once daily	90 mg/day
	H. pylori	Triple therapy: 30 mg PO BID for 10 to 14 days, in combination with amoxicillin and clarithromycin Dual therapy: 30 mg PO TID for 14 days, in combination with amoxicillin	90 mg/day
	Gastric ulcer (including benign and healing of NSAID-associated gastric ulcers); Treatment of erosive esophagitis	**Adult** 30 mg PO once daily (treatment duration varies) **Pediatric** <u>Age 1-11 years</u> Weight ≤ 30 kg: 15 mg PO once daily Weight > 30 kg : 30 mg PO once daily <u>Age 12-17 years</u> 15 to 30 mg PO once daily	30 mg/day

	Risk reduction of NSAID-associated gastric ulcers; Symptomatic GERD; Maintenance of healing of erosive esophagitis	15 mg PO once daily (treatment duration varies)	15 mg/day
	Pathological hypersecretory conditions, including Zollinger-Ellison Syndrome	60 mg PO once daily to 90 mg/day PO BID	180 mg/day
omeprazole/ sodium bicarbonate (Zegerid®, Zegerid® OTC)	Duodenal ulcer; Symptomatic GERD; Erosive esophagitis (treatment and maintenance)	20 mg PO once daily (treatment duration varies)	40 mg/day
	Benign gastric ulcer	40 mg PO once daily	40 mg/day
	Reduction of risk of upper GI bleeding in critically ill patients	40 mg oral suspension only: 40 mg PO initially, 6 to 8 hours later, then daily for 14 days	40 mg/day
esomeprazole strontium	Treatment of erosive esophagitis; Risk reduction of NSAID-associated gastric ulcers	24.65 to 49.3 mg PO once daily (treatment duration varies)	49.3 mg/day
	Symptomatic GERD; Maintenance of healing of erosive esophagitis	24.65 mg PO once daily	24.65 mg/day
	H. pylori triple therapy	49.3 mg PO once daily for 10 days	49.3 mg/day
	Pathological hypersecretory conditions, including Zollinger-Ellison Syndrome	49.3 mg PO BID	240 mg/day

Dosage Forms

Drug Name	Availability
rabeprazole (Aciphex®)	Tablets, delayed release: 20 mg
rabeprazole (Aciphex® sprinkle)	Capsules, delayed release: 5 mg, 10 mg
dexlansoprazole (Dexilant®)	Capsules, delayed release: 30 mg, 60 mg
esomeprazole (Nexium®)	• Capsules, delayed release: 20 mg, 40 mg • Packets, powder for delayed-release oral suspension: 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg
lansoprazole (Prevacid® solutabs™)	Tablets, delayed release orally disintegrating: 15 mg, 30 mg
omeprazole (Prilosec® packets)	Packets, powder for delayed-release oral suspension: 2.5 mg, 10 mg
omeprazole/sodium bicarbonate (Zegerid®)	• Capsules: 20 mg/1100 mg, 40 mg/1100 mg • Unit-dose packets for oral suspension: 20 mg/1680 mg, 40 mg/1680 mg
esomeprazole strontium	Capsules, delayed release: 49.3 mg (equivalent to 40 mg esomeprazole)
Available OTC products	
omeprazole/sodium bicarbonate (Zegerid® OTC)	Capsules: 20 mg/1100 mg
esomeprazole (Nexium® 24HR)	Tablets, delayed release: 20 mg
esomeprazole (Nexium® 24HR clearminis™)	Capsules, delayed release: 20 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. All Indications (must meet all)**:**

1. Prescribed for one of the following uses (a – e):
   a. Symptomatic GERD, including heartburn or laryngopharyngeal reflux;
   b. Esophageal complications of GERD (e.g., erosive esophagitis, esophageal stricture, Barrett's esophagus, and Schatzki's ring);
   c. Extra-esophageal complications (e.g., laryngopharyngeal reflux, vocal cord damage/nodules, asthma, laryngitis and pharyngitis);
   d. Peptic ulcer disease (e.g., gastric ulcers, duodenal ulcers, *H. pylori* and Zollinger- Ellison Syndrome);
   e. Gastrointestinal bleed prophylaxis for NSAID use and member meets at least one of the following (i, ii, or iii):
      i. History of peptic ulcer disease;

ii. Age 60 years or older;
iii. Concurrent therapy with anticoagulants (e.g., warfarin, aspirin, clopidogrel) or oral corticosteroids (e.g., prednisone);

2. For lansoprazole disintegrating tablets or AcipHex Sprinkle: age 1 year or older;
3. Member meets any of the following (a, b, c, or d):
   a. Age less than 12 years and request is for lansoprazole disintegrating tablets, AcipHex Sprinkle, or Prilosec® packets;
   b. Presence of G-tube or significant dysphagia and request is for Prilosec® packets, or omeprazole/sodium bicarbonate: failure of a ≥ 4-week trial of Protonix® packets at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced (chart note documentation may be required);
   c. Currently on clopidogrel and request is for Dexilant®: Failure of a ≥ 4-week trial of pantoprazole tablets at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   d. Request is for Dexilant®, esomeprazole, lansoprazole disintegrating tablets, omeprazole suspension, omeprazole/sodium bicarbonate, rabeprazole: failure of a ≥ 4-week trial of all of the following preferred generic PPIs at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced: omeprazole capsules, pantoprazole tablets, and lansoprazole capsules;
4. For BID dosing requests of non-preferred agents for conditions other than *H. pylori* or pathological hypersecretory conditions, including Zollinger-Ellison Syndrome: member must be titrated up from once daily dosing;
5. Dose does not exceed the FDA-approved maximum recommended dose (refer to Dosing Information).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the FDA-approved maximum recommended dose (refer to Dosing Information).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
ES: esomeprazole strontium
EE: erosive esophagitis
FDA: Food and Drug AdministrationGERD: gastroesophageal reflux disease
GI: gastrointestinal
H. pylori: Helicobacter pylori
NSAID: non-steroidal anti-inflammatory drug
PPI: proton pump inhibitor
TIN: tubulointerstitial nephritis

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
pantoprazole tablets and suspension (Protonix)	**Short-term treatment of erosive esophagitis associated with GERD** Adult and pediatric (age ≥ 5 years and weight ≥ 40 kg): 40 mg PO once daily Pediatric (age ≥ 5 years and weight ≥ 15 kg to < 40 kg): 20 mg PO once daily **Maintenance of healing of erosive esophagitis** 40 mg PO once daily **Pathological hypersecretory conditions, including Zollinger-Ellison Syndrome** 40 mg PO BID	40 mg/day (240 mg/day for pathological hypersecretory conditions)
omeprazole capsules (Prilosec®)	**Duodenal ulcer** 20 mg PO once daily **Symptomatic GERD; Erosive esophagitis (treatment and maintenance)** Adult: 20 mg PO once daily Pediatric (age 1 to 16 years): Weight 5 kg to < 10 kg: 5 mg Weight 10 kg to < 20 kg: 10 mg Weight ≥ 20 kg: 20 mg Pediatric (age 1 month to < 1 year): Weight 5 kg to < 10 kg: 5 mg Weight ≥ 10 kg: 10 mg	40 mg/day (360 mg/day for pathological hypersecretory conditions)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	H. pylori Triple therapy: 20 mg PO BID for 10 days, in combination with amoxicillin and clarithromycin Dual therapy: 40 mg PO once daily for 14 days, in combination with clarithromycin 40 mg/day **Gastric ulcer** 40 mg PO once daily **Pathological hypersecretory conditions, including Zollinger-Ellison Syndrome** 60 mg PO once daily to 80 mg/day PO in divided doses	
lansoprazole capsules (Prevacid®)	**Duodenal ulcers, risk reduction of NSAID-associated gastric ulcer, maintenance of healing of erosive esophagitis** 15 mg PO once daily **Short-term treatment of symptomatic GERD and erosive esophagitis** Adult: 15 to 30 mg PO once daily Pediatric (age 1 to 11 years): Weight > 30 kg: 30 mg PO once daily Weight ≤ 30 kg: 15 mg PO once daily Pediatric (age 12 to 17 years): Non-erosive GERD: 15 mg Erosive esophagitis: 30 mg ***H. pylori*** Triple therapy: 30 mg PO BID for 10 or 14 days in combination with amoxicillin and clarithromycin Dual therapy: 30 mg PO TID for 14 days in combination with amoxicillin **Benign gastric ulcer, healing of NSAID-associated gastric ulcer** 30 mg PO once daily	30 mg/day (180 mg/day for pathological hypersecretory conditions)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Pathological hypersecretory conditions, including Zollinger-Ellison Syndrome 60 mg PO once daily	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - All agents: hypersensitivity (e.g., to drug or other PPIs, substituted benzimidazoles, or to any components of the formulation).
  - AcipHex/Aciphex Sprinkle and Dexilant®: coadministration with rilpivirine- containing products.
  - Refer to the Contraindications section of the prescribing information for clarithromycin and amoxicillin, when administered in combination with Aciphex® (only for Aciphex®).

- Boxed Warning(s):
  - none reported.

APPENDIX D: General Information

- Dexilant® 60 mg vs. Prevacid® 30 mg in EE was evaluated in two studies. Non-inferiority was demonstrated in both studies, but superiority was demonstrated in only one study.
- Dexilant® 90 mg was studied and did not provide additional clinical benefit over Dexilant® 60 mg in EE.
- Patients with a platelet reactivity index (PRI) >50% is linked to sub-acute stent thrombosis.
- In a study by Siller-Matula JM, et al., The PRI was similar in patients on Protonix or Nexium® (mean 51%; 95% CI 48-54%) and for patients on Plavix and Protonix the mean was PRI = 50% and for Plavix and Nexium® the mean PRI was 54%.
- Over 90% of gastric and duodenal ulcers heal within 8 weeks of PPI therapy.
- There have been models constructed to evaluate both the efficacy and cost-effectiveness of "step-up" therapy (starting with H2 antagonists and titrating to symptom control) and "step-down therapy" (starting with PPI therapy and decreasing therapy to the lowest form of acid suppression that controls symptoms). Neither method has been proven superior.
- Patients with PUD (DU or GU) should be tested for H. pylori and treated, if positive.
- For Laryngopharyngeal reflux (LPR), the American Academy of Otolaryngology recommends twice-daily dosing with PPIs for a minimum period of 6 months with the possibility of chronic treatment. BID dosing

of PPIs has been shown to be superior to once daily dosing in LPR.

- Two capsules of Zegerid® 20 mg are not interchangeable with one capsule of Zegerid® 40 mg because each capsule or packet contains the same amount of sodium bicarbonate.
- Pediatric patients: The safety and efficacy of Dexilant®, Zegerid® and Protonix in children have not been established. The safety and efficacy of Prevacid® have been established in pediatric patients 1 to 17 years of age. The safety and efficacy of omeprazole have been established in pediatric patients 1 to 16 years of age. The safety and efficacy of Nexium® have been established in pediatric patients 1 to 17 years of age for up to 8 weeks. The safety and efficacy of Aciphex® have been established in pediatric patients 1 year and older for up to 36 weeks.
- Safety and efficacy of proton pump inhibitors have not been established in patients less than 1 year of age. Lansoprazole was no more effective than placebo in patients 1 month to less than 1 year of age with symptomatic GERD in a multi-center, double-blind, placebo-controlled study (Orenstein et al, 2009). Studies with Aciphex® Sprinkle do not support its use for the treatment of GERD in pediatric patients younger than 1 year of age.
- Prevacid® has a non-FDA-approved, Class IIa strength recommendation for giant duodenal ulcer per Micromedex. Of 27 study patients with giant duodenal ulcer placed on Prilosec®, 20 (71.4%) did not require operative intervention, and 8 (28.6%) required operation for ulcer complications.
- Prevacid® has a non FDA-approved, Class IIa strength recommendation for heartburn and H. pylori uadruple therapy per Micromedex.
- Aciphex® has a non FDA-approved, Class II a strength recommendation for gastric ulcers, H. pylori quadruple therapy and indigestion per Micromedex.
- Several published observational studies suggest that high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer) may be associated with an increased risk for osteoporosis related fractures. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.
- According to their respective package inserts, concomitant administration of either pantoprazole or dexlansoprazole with clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel- induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of Protonix or Dexilant®. American Hospital Formulary Service Drug Information further states, “If concomitant proton-pump inhibitor therapy [with clopidogrel] is considered necessary, some clinicians suggest the use of pantoprazole, which appears to be the weakest inhibitor of cytochrome P450 2C19 (CYP2C19) among proton-pump inhibitors.”
- Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Discontinue Drug and evaluate patients with suspected acute TIN.

References

1. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2008;52(18):1502-1517. Accessed January 28, 2021.
2. Laine L and Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol 2012; 107:345-360. Accessed January 28, 2021.

3. Devault K, Castell D. Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease. Am J Gastroenterol 2005;100:190-200. Accessed January 28, 2021.
4. Wang K, Sampliner R. Updated Guidelines for the Diagnosis, Surveillance, and Therapy of Barrett's Esophagus. Am J Gastroenterol 2008;103:788-797. Accessed January 28, 2021.
5. Laryngopharyngeal reflux: Position statement of the Committee on Speech, Voice, and Swallowing Disorders of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngology-Head and Neck Surgery. 2002;127:30-35. Accessed January 28, 2021.
6. Laryngopharyngeal Reflux: Prospective Cohort Study Evaluating Optimal Dose of Proton- Pump Inhibitor Therapy and Pretherapy Predictors of Response. Laryngoscope. 2005; 115. Accessed January 28, 2021.
7. Lanas A. Potent gastric acid inhibition in the management of Barrett's oesophagus. Drugs. 2005;65 Suppl 1:75-82.
8. Spechler, S. Barrett's Esophagus. N Engl J Med. 2002;346:836-842. Accessed January 28, 2021.
9. Katz PO, Gerson L, Vela M. Guidelines for the diagnosis and management of gastroesophageal reflux disease. American Journal of Gastroenterology. 2013;108(3):308- 328. Accessed January 28, 2021.
10. AcipHex® Prescribing Information. Woodcliff Lake, NJ: Eisai, Inc; November 2020. Available at: https://www.Aciphex®.com/. Accessed January 28, 2021.
11. AcipHex® Sprinkle Prescribing Information. Research Triangle Park, NC: Aytu Therapeutics, LLC; November 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204736s012lbl.pdf. Accessed January 28, 2021.
12. Dexilant® Prescribing Information. Lexington, MA: Takeda Pharmaceuticals America, Inc; November 2020. Available at: https://general.takedapharm.com/DEXILANT®PI. Accessed January 28, 2021.
13. Nexium® Prescribing Information. Wilmington, DE: AstraZeneca; November 2020. Available at: https://www.Nexiumtouchpoints.com/. Accessed January 28, 2021.
14. Prevacid® Prescribing Information. Lexington, MA: Takeda Pharmaceuticals; November 2020. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=71ba78cb-7e46-43eb-9425-fa130f537f84. Accessed January 28, 2021.
15. Prilosec® Prescribing Information. Wilmington, DE: AstraZeneca; August 2018. Available at: https://www.Prilosecpackets.com/HCP/Indications. Accessed January 28, 2021.
16. Zegerid® Prescribing Information. Bridgewater, NJ: Valeant Pharmaceuticals; June 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021849s014,021636s019lbl.pdf. Accessed January 28, 2021.
17. Esomeprazole strontium Prescribing Information. Carmel, IN: ParaPRO LLC; June 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202342s005lbl.pdf. Accessed January 28, 2021.
18. Protonix Prescribing Information. Philadelphia, PA: Pfizer Inc.; June 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020987s054,022020s016,02098 8s060lbl.pdf. Accessed January 28, 2021.
19. Rabeprazole, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed January 28, 2021.
20. Dexlansoprazole, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed January 28, 2021.
21. Esomeprazole, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed January 28, 2021.
22. Omeprazole, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed January 28, 2021.
23. Lansoprazole, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed January 28, 2021.
24. Omeprazole and Sodium Bicarbonate, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed January 28, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
2Q2020 P&T Review; No updates, references reviewed and updated	4/2020	05/20/2020
Policy was reviewed: 1. Line of business policy applies was updated to All lines of business. 2. Prevacid was removed from this policy. 3. Dosage Forms was updated as esomeprazole strontium 24.65 mg was discontinued . 4. Continued therapy approval criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 5. Approval durations were updated to 12 months from Length of Benefit. 6. Appendix A was updated. 7. Appendix B: Therapeutic Alternatives header verbiage has been changed to "*Below are suggested therapeutic alternatives based on…"* 8. Appendix D was updated. 9. References were updated.	01/28/2021	03/09/2021