

## AN UPDATE TO DUR RECOMMENDATIONS FOR PROTON PUMP INHIBITOR DEPRESCRIBING IN MISSISSIPPI MEDICAID

### BACKGROUND

During the March 2018 DUR Board meeting the use of proton pump inhibitors (PPIs) in the Medicaid population was reviewed examining the potential of deprescribing these products. The Board recommended the implementation of a maximum days supply edit of 90 days in a 12-month period for the use of PPIs based on diagnosis. Due to the prioritized implementation of opioid criteria, the implementation of the PPI maximum days supply edit was postponed. At this time the Division of Medicaid is requesting the DUR Board reevaluate the previous DUR recommendations based on a review of current literature regarding PPI chronic therapy and evaluation of current prescribing trends in Medicaid.

Upper gastrointestinal disorders are increasingly common worldwide. In 2018, 18% to 27% of adults in the United States (US) had gastroesophageal reflux disease (GERD).<sup>1</sup> Increasing incidence of GERD may result in increasing numbers of related complications which include erosive esophagitis (EE), Barrett's esophagus, gastroesophageal strictures, and adenocarcinoma.<sup>2</sup> Proton pump inhibitors (PPIs) are commonly used in clinical practice to treat upper gastrointestinal disorders, including GERD, EE, and gastric ulcers, and make up more than half of the drugs utilized in that market.<sup>3,4</sup> PPIs provide successful symptom relief for 57% to 80% of patients with EE, and over 85% of EE lesions are successfully healed with PPI therapy.<sup>5</sup> In addition to excellent clinical success, patient-reported adverse events of PPIs are mild.<sup>4</sup>

High therapeutic success rates, good tolerability, and patient satisfaction with PPI use have led to high utilization of the drug class.<sup>6</sup> In 2012, PPIs were the second-most commonly prescribed medication class by dollar amount within the US and accounted for \$11 billion of the United States' drug expenditure.<sup>3</sup> Despite common use, concerns with overprescribing and potential long-term adverse events exist. Chronic use of PPIs has been associated with increased risk of osteoporotic fractures, *Clostridium difficile* infection, community-acquired pneumonia, vitamin B12 deficiency, acute gastroenteritis, and dementia.<sup>7-9</sup> Inappropriate use of PPIs carries the potential for both clinical and economic ramifications. In 2010 a large, single-center study found that as many as 36% of patients prescribed PPIs lacked appropriate documentation for PPI therapy with the estimated cost of inappropriate use of PPIs totaled over 1.7 million dollars.<sup>10</sup> Furthermore, unnecessary use places patients at higher risks for adverse events and drug-drug interactions.

Demand for appropriate management of PPI therapy has grown as concerns for these adverse events has risen. Recently, the *Canadian Family Physician* published guidelines that detailed deprescribing practices for patients on potentially unnecessary PPI therapy.<sup>11</sup> However, there is conflicting evidence regarding the causal effect between PPIs and adverse event profiles. Recent studies have suggested that PPI use is not associated with the incidence of dementia, and instead

suggest high body mass index may instead be a predicting factor of dementia onset.<sup>12,13</sup> One study found that antibiotic use, rather than PPI use, was the greatest contributing factor to the incidence of *C. diff* in hospitalized populations.<sup>14</sup> Lack of conclusive evidence regarding adverse events along with potential worsening patient quality of life with tapering PPI therapy may compound provider unwillingness to deprescribe PPIs. Providers have cautioned that rebound acid hypersecretion may occur in some patients, particularly those who have been on long-term PPI therapy. This rebound phenomenon may be partially responsible for chronic PPI use.<sup>15</sup> Intermittent, low-dose, or on-demand PPI use may help minimize cost or adverse event burden in patients who are unable or unwilling to stop therapy.<sup>11</sup> Patients are encouraged to step down from PPI use to histamine-2 receptor antagonist (H2 antagonist) therapy for control of mild upper gastrointestinal disease, as H2 antagonist uses overlap significantly with those of PPIs.<sup>2</sup> While H2 antagonists are less effective and have greater drug tolerance than PPIs, their safety and drug-drug interaction profiles are superior.<sup>2</sup> PPI deprescribing practices promoting utilizing H2 antagonists may be disrupted by recent manufacturing instability among this medication class. In 2019, the H2-antagonists nizatidine and ranitidine were found to contain unacceptable levels of N-nitrosodimethylamine (NMDA), a probable carcinogen.<sup>16</sup> Both products have experienced nationwide recalls in response to manufacturing contamination.<sup>17</sup> Given this news, concern exists that physicians will shift prescribing back to PPIs in spite of risks associated with chronic PPI therapy.

MS-DUR conducted the following:

- An update to the March 2018 DUR Board analyses of prescribing trends for PPIs among Medicaid beneficiaries.
- An analysis for H2 antagonist utilization to assess the impact of market disruption caused by the recent FDA safety notices.

## **METHODS**

A retrospective database analysis was conducted using Medicaid point-of-sale (POS) and medical claims data for fee-for-service (FFS) and coordinated care organizations (CCOs): UnitedHealthcare (UHC), Magnolia Health (MAG) and Molina Healthcare (MOL). Beneficiaries prescribed PPIs and H2 antagonists were identified during the period of September 1, 2018 to August 31, 2019. Descriptive characteristics are presented in Tables 1a and 1b. Pharmacy claims data for the period of September 2018 – November 2019 were analyzed to determine the number of prescription fills for PPIs and H2 antagonists identifying potential prescribing trends (Tables 2a and 2b). For PPI users, length of PPI therapy was identified by measuring days supply after adjusting for early refills with a maximum persistence gap 60 days allowed. The index event was defined as the first paid claim in the study period. Beneficiaries were stratified into two groups based on length of PPI therapy ( $\leq 90$  days and  $> 90$  days). To allow a follow-up period of at least 90 days for all beneficiaries prescribed PPIs during the study period, POS claims through November 2019 were analyzed to measure length of therapy (Tables 3a and 3b). A 24-month look back period was used to identify target diagnoses for PPI use (Table 4).

Occurrences of two common acute conditions that have been associated with PPI use, *Clostridium difficile* (*C. diff*) and acute gastroenteritis (AGE), were identified among beneficiaries after initiating PPI therapy. The ICD-10 codes used to identify *C. difficile* infections were A04.71 and A04.72. The ICD-10 codes used to identify AGE were K52.0, K52.1, K52.21-29, K52.89 and K52.9. Results were stratified by age of the beneficiary and length of PPI therapy (Tables 5 and 6). Recent hospitalizations prior to initiation of PPI therapy were also examined to assess the impact hospitalizations had on PPI therapy initiation. A 30-day look back period prior to the index PPI prescription was used to identify hospitalizations (Table 7).

## RESULTS

Tables 1a/1b display demographic characteristics of beneficiaries prescribed PPIs and H2 antagonists between September 2018 and August 2019.

TABLE 1a: Demographic Characteristics of Beneficiaries Prescribed PPI Therapy (Sep 2018 - Aug 2019)									
Variable	FFS		UHC		Magnolia		Molina		Total
<b>Age Category (yrs)</b>									
0-17	1,868	29.0%	3,299	31.4%	3,461	24.8%	408	27.7%	9,036
18-35	1,053	16.4%	2,114	20.1%	2,852	20.4%	658	44.7%	6,677
36-50	1,108	17.2%	2,356	22.4%	3,338	23.9%	253	17.2%	7,055
51-64	2,405	37.4%	2,743	26.1%	4,324	30.9%	152	10.3%	9,624
<b>Total</b>	<b>6,434</b>		<b>10,512</b>		<b>13,975</b>		<b>1,471</b>		<b>32,392</b>
<b>Gender</b>									
Female	3,945	61.3%	7,065	67.2%	9,708	69.5%	1,116	75.9%	21,834
Male	2,489	38.7%	3,447	32.8%	4,267	30.5%	355	24.1%	10,558
<b>Total</b>	<b>6,434</b>		<b>10,512</b>		<b>13,975</b>		<b>1,471</b>		<b>32,392</b>
<b>Race</b>									
African American	2,823	43.9%	4,673	44.5%	6,737	48.2%	613	41.7%	14,846
Caucasian	3,042	47.3%	4,423	42.1%	5,526	39.5%	632	43.0%	13,623
Hispanic	61	0.9%	145	1.4%	134	1.0%	16	1.1%	356
Other	508	7.9%	1,271	12.1%	1,578	11.3%	210	14.3%	3,567
<b>Total</b>	<b>6,434</b>		<b>10,512</b>		<b>13,975</b>		<b>1,471</b>		<b>32,392</b>

### PPIs:

- 32,392 unique beneficiaries were prescribed PPIs during the study period.
- There was no specific age category that contributed to the majority of prescribing of PPIs.
- Approximately twice as many females received PPIs as compared to males.

TABLE 1b: Demographic Characteristics of Beneficiaries Prescribed H2 Antagonists (Sep 2018 - Aug 2019)									
Variable	FFS		UHC		Magnolia		Molina		Total
<b>Age Category (yrs)</b>									
0-17	2,543	56.6%	6,270	69.9%	6,970	62.4%	1,413	64.76%	<b>17,196</b>
18-35	705	15.7%	1,249	13.9%	1,679	15.0%	586	26.86%	<b>4,219</b>
36-50	387	8.6%	708	7.9%	1,131	10.1%	125	5.73%	<b>2,351</b>
51-64	859	19.1%	749	8.3%	1,392	12.5%	58	2.66%	<b>3,058</b>
<b>Total</b>	<b>4,494</b>		<b>8,976</b>		<b>11,172</b>		<b>2,182</b>		<b>26,824</b>
<b>Gender</b>									
Female	2,601	57.9%	5,365	59.8%	6,825	61.1%	1,427	65.40%	<b>16,218</b>
Male	1,893	42.1%	3,611	40.2%	4,347	38.9%	755	34.60%	<b>10,606</b>
<b>Total</b>	<b>4,494</b>		<b>8,976</b>		<b>11,172</b>		<b>2,182</b>		<b>26,824</b>
<b>Race</b>									
African Amer	1,916	42.6%	3,396	37.8%	4,938	44.2%	746	34.19%	<b>10,996</b>
Caucasian	1,948	43.3%	2,973	33.1%	3,423	30.6%	576	26.40%	<b>8,920</b>
Hispanic	59	1.3%	165	1.8%	162	1.5%	12	0.55%	<b>398</b>
Other	571	12.7%	2,442	27.2%	2,649	23.7%	848	38.86%	<b>6,510</b>
<b>Total</b>	<b>4,494</b>		<b>8,976</b>		<b>11,172</b>		<b>2,182</b>		<b>26,824</b>

## H2 antagonists:

- 26,824 unique beneficiaries were prescribed H2 antagonists during the study period.
- Children age 17 and under received 64.1% (n=17,196) of the H2 antagonists prescribed.

With increased awareness surrounding PPI deprescribing in general among healthcare professionals in recent years, a downward trend in PPI prescribing could potentially be expected. Table 2a depicts PPI prescription fills by month.

TABLE 2a: PPI Prescription Fills by Month and Plan (Sep 2018 - Nov 2019)					
Month	Plan				Total
	FFS	UHC	Magnolia	Molina	
Sep-18	2,009	3,336	4,924	0	10,269
Oct-18	2,139	3,347	5,212	13	10,711
Nov-18	2,030	3,227	4,979	2	10,238
Dec-18	1,942	3,073	4,760	2	9,777
Jan-19	2,059	3,308	5,079	2	10,448
Feb-19	1,901	3,046	4,635	1	9,583
Mar-19	2,013	3,048	4,809	120	9,990
Apr-19	2,107	3,164	4,862	443	10,576
May-19	2,093	3,076	4,887	483	10,539
Jun-19	1,912	2,908	4,548	476	9,844
Jul-19	2,078	3,231	4,896	594	10,799
Aug-19	2,144	3,123	4,891	661	10,819
Sep-19	2,032	2,922	4,671	606	10,231
Oct-19	2,209	3,127	4,910	698	10,944
Nov-19	2,083	2,916	4,830	750	10,579
<b>Total</b>	<b>30,751</b>	<b>46,852</b>	<b>72,893</b>	<b>4,851</b>	<b>155,347</b>

- Previous March 2018 DUR Board Report analyses indicated the average number of PPI prescriptions filled monthly for calendar year 2017 was 10,563.<sup>18</sup>
- Current March 2020 DUR Board report analyses indicate the average number of PPI prescriptions filled monthly between September 2018 and November 2019 was **10,356**.
- Minimal change was noted in the monthly volumes of PPI prescribed for the two analyses timeframes.

## H2-Antagonist Prescribing

Due to manufacturing issues with the presence of unacceptable issues and subsequent FDA recalls initiated in September 2019, the use of H2 antagonists could be impacted. Table 2b illustrates a decline in H2 antagonist prescription numbers correlating with the FDA recalls.

Month	Plan				Total
	FFS	UHC	Magnolia	Molina	
Sep-18	1,084	1,674	2,244	0	5,002
Oct-18	1,198	1,759	2,421	8	5,386
Nov-18	1,024	1,601	2,183	1	4,809
Dec-18	958	1,474	2,097	3	4,532
Jan-19	1,140	1,808	2,377	0	5,325
Feb-19	1,051	1,518	2,076	3	4,648
Mar-19	1,056	1,561	2,164	123	4,904
Apr-19	1,130	1,524	2,122	380	5,156
May-19	1,112	1,430	2,102	457	5,101
Jun-19	1,006	1,256	1,867	459	4,588
Jul-19	1,156	1,429	2,003	619	5,207
Aug-19	1,151	1,483	2,093	727	5,454
Sep-19	1,097	1,377	1,914	713	5,101
Oct-19	1,085	1,350	1,877	652	4,964
Nov-19	899	981	1,434	469	3,783
<b>Total</b>	<b>16,147</b>	<b>22,225</b>	<b>30,974</b>	<b>4,614</b>	<b>73,960</b>

- H2 antagonist prescription claims began decreasing in November 2019.
  - The number of prescription fills in November 2019 (3,783) represented a 24.5% decrease from the average number of monthly prescription fills between September 2018 and October 2019.

*\*It should be noted that the analysis period ended early during the FDA recall period for ranitidine. However with the data available, it does not appear the recall of ranitidine products corresponded to an immediate increase in PPI prescribing.*

## PPI Prescribing Trends

Table 3 describes characteristics of beneficiaries prescribed PPIs based on length of therapy.

- 65.6% (N=21,325) of beneficiaries prescribed PPIs during the study period had a length of therapy  $\leq$  90 days.
- As the age of beneficiaries increased, the percent with a length of therapy > 90 days increased overall.
- Although Molina had the highest percentage of beneficiaries with a length of therapy  $\leq$  90 days at 82.5%, there was a significantly smaller number of beneficiaries who received PPIs during the study period in Molina compared to the other plans. Molina's initial Mississippi Medicaid implementation date of 10-01-2018 yielded smaller total PPI numbers and less initial beneficiaries enrolled for comparison purposes during the study period.

<b>TABLE 3: Demographic Characteristics of Beneficiaries Prescribed PPIs Stratified by Length of Therapy (Sep 2018 - Aug 2019)</b>					
<b>Characteristic</b>	<b>Length of Therapy <math>\leq</math> 90 days (N=21,325)</b>		<b>Length of Therapy &gt; 90 days (N= 11,067)</b>		<b>Total (N=32,392)</b>
<b>Age Category</b>					
0-17	7,045	78.0%	1,991	22.0%	9,036
18-35	5,101	76.4%	1,576	23.6%	6,677
36-50	4,278	60.6%	2,777	39.4%	7,055
51-64	4,901	50.9%	4,723	49.1%	9,624
<b>Sex</b>					
Female	14,683	67.2%	7,151	32.8%	21,834
Male	6,642	62.9%	3,916	37.1%	10,558
<b>Race</b>					
Caucasian	8,355	61.3%	5,628	41.3%	13,623
Other	2,223	62.3%	1,344	37.7%	3,567
Hispanic	296	83.1%	60	16.9%	356
African American	10,451	70.4%	4,395	29.6%	14,846
<b>Plan</b>					
Fee-for-service	3,977	61.8%	2,457	38.2%	6,434
UHC	7,275	69.2%	3,237	30.8%	10,512
Magnolia	8,860	63.4%	5,115	36.6%	13,975
Molina	1,213	82.5%	258	17.5%	1,471

Various PPIs available along with their FDA-approved and compendia supported indications for use are provided in Figure 1. Indications for PPI use influence duration of therapy.

FIGURE 1 – PPI FDA-approved and compendia supported indications

Micromedex® Recommendations for PPI Medications		
Generic (Brand) Product	FDA Indications	Compendia-Supported Indication
Omeprazole (Prilosec)	<ul style="list-style-type: none"> <li>Erosive esophagitis</li> <li>Gastric hypersecretion</li> <li>Acute gastric ulcer</li> <li>Symptomatic GERD</li> <li>Acute duodenal ulcer</li> </ul>	<ul style="list-style-type: none"> <li>Duodenal ulcer maintenance</li> <li>Indigestion</li> <li>Giant duodenal ulcer</li> <li>GI hemorrhage</li> <li>Refractory GERD</li> <li><i>H. pylori</i>-induced duodenal ulcer</li> <li>Esophageal stricture</li> <li>Prophylaxis of NSAID-induced gastric ulcer</li> </ul>
Esomeprazole (Nexium)	<ul style="list-style-type: none"> <li>Erosive esophagitis</li> <li>Prophylaxis of NSAID-induced gastric ulcer</li> <li>Symptomatic GERD</li> <li>Zollinger-Ellison syndrome</li> <li><i>H. pylori</i>-induced duodenal ulcer</li> </ul>	<ul style="list-style-type: none"> <li>Post-procedure endoscopic application of hemostyptics to gastric lesion</li> </ul>
Pantoprazole (Protonix)	<ul style="list-style-type: none"> <li>Erosive esophagitis</li> <li>Gastric hypersecretion</li> <li>Zollinger-Ellison syndrome</li> </ul>	<ul style="list-style-type: none"> <li>Prophylaxis of NSAID-induced gastric ulcer</li> <li><i>H. pylori</i> GI tract infection</li> <li>Acute duodenal ulcer</li> </ul>
Lansoprazole (Prevacid)	<ul style="list-style-type: none"> <li>Erosive esophagitis</li> <li>Acute gastric ulcer</li> <li>Treatment of NSAID-induced gastric ulcer</li> <li>Prophylaxis of NSAID-induced gastric ulcer</li> <li>Symptomatic GERD</li> <li><i>H. pylori</i> GI tract infection</li> <li>Acute duodenal ulcer</li> <li>Zollinger-Ellison syndrome</li> <li>Duodenal ulcer maintenance</li> </ul>	<ul style="list-style-type: none"> <li>Barrett's esophagus</li> <li>Gastric ulcer maintenance</li> <li>Indigestion</li> </ul>
Dexlansoprazole (Dexilant)	<ul style="list-style-type: none"> <li>Erosive esophagitis</li> <li>Non-erosive symptomatic GERD</li> </ul>	<ul style="list-style-type: none"> <li>Refractory GERD</li> </ul>
Rabeprazole (Aciphex)	<ul style="list-style-type: none"> <li>Gastric hypersecretion</li> <li>Symptomatic GERD</li> <li>Acute duodenal ulcer</li> <li><i>H. pylori</i>-induced duodenal ulcer</li> </ul>	<ul style="list-style-type: none"> <li>Acute gastric ulcer</li> <li>Indigestion</li> <li>Laryngopharyngeal reflux</li> <li><i>H. pylori</i>-induced peptic ulcer</li> </ul>

Based on manufacturer recommendations and published research, recommended lengths of therapy for FDA-approved and compendia supported indications are displayed in Figure 2.

FIGURE 2: Recommended lengths of therapy with PPI treatment according to indication.<sup>6,19–24</sup>

Common Length of Therapy	FDA and Compendium-Supported Indications for PPI
<b>Long-term</b> (> 90 days)	Los Angeles Grade C or D erosive esophagitis (Moderate-Severe)
	Esophageal stricture
	Gastric hypersecretion
	Zollinger-Ellison syndrome
	Refractory GERD
	Prophylaxis of NSAID-induced gastric ulcer
	Barrett’s esophagus
	Gastric ulcer maintenance
	Duodenal ulcer maintenance
<b>Short-term</b> (≤ 90 days)	Los Angeles Grade A or B Erosive Esophagitis (Mild)
	<i>H. pylori</i> GI tract infection
	<i>H. pylori</i> -induced duodenal ulcer
	<i>H. pylori</i> -induced peptic ulcer
	Acute gastric ulcer
	Acute duodenal ulcer
	Symptomatic GERD
	Giant duodenal ulcer
	Post-procedure endoscopic application of hemostyptics to gastric lesion
	Treatment of NSAID-induced gastric ulcer
	Indigestion
	GI hemorrhage
	Non-erosive symptomatic GERD
	Laryngopharyngeal reflux

GI = gastrointestinal; GERD = Gastroesophageal reflux disease; *H. pylori* = *Helicobacter pylori*; NSAID = nonsteroidal anti-inflammatory drug

Table 4 includes information about the presence of target diagnoses present for beneficiaries prescribed PPIs during the study period. To determine the presence of target diagnoses, a medical claim had to occur with associated diagnoses within 24 months prior to the index prescription date.

- Approximately 27.3% (n=8847) of beneficiaries prescribed PPIs did not have a target diagnosis present in medical claims data. **This is a major improvement from the data reported in the March 2018 DUR report where 62.5% of beneficiaries did not have a target diagnosis present.**
- Of the beneficiaries prescribed PPIs with diagnoses indicating short-term therapy, 38.7% took PPIs for > 90 days.

**TABLE 4: Presence of Target Diagnosis and Length of Time on Therapy for Beneficiaries Prescribed PPI Therapy (Sep 2018 - Aug 2019)**

Target Diagnosis*	FFS (n=6,434)					UHC (n=10,512)					Magnolia (n=13,975)					Molina (n=1,471)				
	Total with Dx	Length of Therapy				Total with Dx	Length of Therapy				Total with Dx	Length of Therapy				Total with Dx	Length of Therapy			
		≤ 90 days	> 90 days	≤ 90 days	> 90 days		≤ 90 days	> 90 days	≤ 90 days	> 90 days		≤ 90 days	> 90 days	≤ 90 days	> 90 days					
Esophagitis (GERD)	3,493	1,939	55.5%	1,554	44.5%	7,310	4,745	64.9%	2,565	35.1%	9,918	5,826	58.7%	4,092	41.3%	744	596	80.1%	148	19.9%
GERD	3,275	1,811	55.3%	1,464	44.7%	6,828	4,395	64.4%	2,434	35.6%	9,414	5,484	58.3%	3,930	41.7%	699	558	79.8%	141	20.2%
GI bleed	330	200	60.6%	130	39.4%	362	242	66.9%	120	33.1%	410	242	59.0%	168	41.0%	32	25	78.1%	7	21.9%
<i>H. pylori</i> infection	199	137	68.8%	62	31.2%	467	352	75.4%	115	24.6%	689	510	74.0%	179	26.0%	41	38	92.7%	3	7.3%
Stress ulcer	194	103	53.1%	91	46.9%	359	251	69.9%	108	30.1%	413	229	55.4%	184	44.6%	15	13	86.7%	2	13.3%
Gastric ulcer	164	103	62.8%	61	37.2%	315	201	63.8%	114	36.2%	373	233	62.5%	140	37.5%	23	18	78.3%	5	21.7%
NSAID use	149	91	61.1%	58	38.9%	289	186	64.4%	103	35.6%	439	249	56.7%	193	44.0%	17	11	64.7%	6	35.3%
Barett's esophagus	50	26	52.0%	24	48.0%	99	46	46.5%	53	53.5%	152	71	46.7%	81	53.3%	2	1	50.0%	1	50.0%
Erosive esophagitis	13	8	61.5%	5	38.5%	20	13	65.0%	7	35.0%	21	14	66.7%	7	33.3%	6	6	100.0%	0	0.0%
Zollinger-Ellison	1	0	0.0%	1	100.0%	1	1	100.0%	0	0.0%	1	1	100.0%	0	0.0%	0	0	0.0%	0	0.0%
Other target dianoses**	560	323	57.7%	245	43.8%	1,277	855	67.0%	422	33.0%	1,747	1,078	61.7%	669	38.3%	91	76	83.5%	15	16.5%
<b>NO TARGET DIAGNOSIS</b>	<b>2,105</b>	<b>1,440</b>	<b>68.4%</b>	<b>665</b>	<b>31.6%</b>	<b>2,681</b>	<b>2,108</b>	<b>78.6%</b>	<b>573</b>	<b>21.4%</b>	<b>3,411</b>	<b>2,518</b>	<b>73.8%</b>	<b>893</b>	<b>26.2%</b>	<b>650</b>	<b>549</b>	<b>84.5%</b>	<b>101</b>	<b>15.5%</b>

NOTE 1: Beneficiaries taking PPIs may be included in more than one diagnosis category, except the 'no target diagnosis' category.  
NOTE 2: 585 beneficiaries did not have medical claims to record target diagnoses.  
NOTE 3: Green highlight represents target diagnoses with indications for long-term PPI use. Orange highlight represents target diagnoses with indication for short-term therapy where beneficiaries received PPI therapy > 90 days.  
\*Diagnosis code was recorded in a medical claim within 24 months of starting PPI therapy.  
\*\* Other diagnoses include achalasia and cardiospasm, duodenal ulcer, dyskinesia esophagus, esophageal hemorrhage, gastritis and duodenitis, gastroesophageal laceration-hemorrhage syndrome, gastrojejunal ulcer, malignant mast cell tumors, multiple endocrine neoplasia, neoplasm of uncertain behavior of other and unspecified endocrine glands, peptic ulcer unspecified, perforation of esophagus, stricture and stenosis of esophagus

Chronic use of PPIs has been associated with an increased risk of multiple adverse events (AE). Two acute AEs associated with chronic PPI use are *clostridium difficile* (*C.diff*) infection and acute gastroenteritis (AGE). A recent study published in the Journal of the American Medical Association found that continuous PPI use was associated with an increased risk of developing AGE of viral origin.<sup>9</sup> Approximately 19-21 million cases of AGE annually can be linked to viral infections in the US.<sup>25,26</sup> An estimated 500,000 Americans are infected with *C.diff* annually, of which approximately 41% are community-acquired cases.<sup>27</sup> Using the June 2019 US Census estimate of 328,234,721 for the US population<sup>28</sup>, the calculated incidence proportion of AGE was approximately 6.4%, all-cause *C.diff* was approximately 0.15% and community-acquired *C.diff* was 0.062% in 2019. In Tables 5 and 6, the number of beneficiaries that experienced *C.diff* infections and AGE after being prescribed PPI therapy was examined.

TABLE 5: Number of Beneficiaries with Claims for <i>Clostridium difficile</i> Infection After Prescription for PPI (Sep 2018 - Nov 2019)									
Age Category	FFS (n=6,434)		UHC (n=10,512)		Magnolia (n=13,975)		Molina (n=1,471)		Total
	Length of Therapy		Length of Therapy		Length of Therapy		Length of Therapy		
	≤ 90 days	> 90 days	≤ 90 days	> 90 days	≤ 90 days	> 90 days	≤ 90 days	> 90 days	
0-17 years	3	0	3	4	5	4	1	0	20
18-35 years	4	2	1	2	3	1	1	1	15
36-50 years	8	2	4	4	4	8	0	0	30
51-64 years	19	10	12	6	11	5	1	0	64
<b>Total</b>	<b>34</b>	<b>14</b>	<b>20</b>	<b>16</b>	<b>23</b>	<b>18</b>	<b>3</b>	<b>1</b>	<b>129</b>

TABLE 6: Number of Beneficiaries with Claims for Acute Gastroenteritis After Prescription for PPI (Sep 2018 - Nov 2019)									
Age Category	FFS (n=6,434)		UHC (n=10,512)		Magnolia (n=13,975)		Molina (n=1,471)		Total
	Length of Therapy		Length of Therapy		Length of Therapy		Length of Therapy		
	≤ 90 days	> 90 days	≤ 90 days	> 90 days	≤ 90 days	> 90 days	≤ 90 days	> 90 days	
0-17 years	54	22	236	74	229	91	30	10	746
18-35 years	47	14	107	29	148	59	21	7	432
36-50 years	41	27	90	57	121	94	8	3	441
51-64 years	54	52	91	59	90	130	4	3	483
<b>Total</b>	<b>196</b>	<b>115</b>	<b>524</b>	<b>219</b>	<b>588</b>	<b>374</b>	<b>63</b>	<b>23</b>	<b>2,102</b>

NOTE for Table 4 and Table 5: 1,453 beneficiaries (4.48%) did not have medical claims available for outcome evaluation. Outcome evaluation was conducted in period following first prescription of PPI till Nov 2019

- Of the total cohort of 32,392 beneficiaries prescribed PPI therapy,
  - 129 (0.4%) had *C. diff* infection and
  - 2,102 (6.5%) had AGE during the study period.
    - There was virtually no difference in proportions experiencing *C.diff* infections or AGE based of length of PPI therapy (≤ 90 days or > 90 days).

PPIs are commonly prescribed in the inpatient setting as a continuation of outpatient use or for stress ulcer prophylaxis. Upon discharge from the hospital, PPIs are often continued even when there is no indication for continued use. Table 7 examines the presence of a recent inpatient hospitalization prior to an initial PPI prescription during the study period.

TABLE 7: Summary of Hospitalizations in a 30-day Period Prior to PPI Therapy Index Date (Sep 2018 - Aug 2018)									
Age Category	FFS		UHC		Magnolia		Molina		Total
	Prior Hospitalization		Prior Hospitalization		Prior Hospitalization		Prior Hospitalization		
	0- 14 days	15 - 30 days	0- 14 days	15 - 30 days	0- 14 days	15 - 30 days	0- 14 days	15 - 30 days	
0-17 years	16	16	32	34	47	35	14	12	206
18-35 years	43	30	57	21	92	48	18	13	322
36-50 years	61	38	64	23	98	42	9	3	338
51-64 years	162	105	120	44	174	102	21	5	733
<b>Total</b>	<b>282</b>	<b>189</b>	<b>273</b>	<b>122</b>	<b>411</b>	<b>227</b>	<b>62</b>	<b>33</b>	<b>1599</b>

- A total of 1,599 beneficiaries (4.9%) with 1,712 hospitalizations initiated PPI therapy within 30 days after a hospitalization.
  - *For the 113 beneficiaries with multiple hospitalizations in a 30-day period prior to initiation of a PPI, the hospitalization closest to the PPI index date was used in determining the number of days.*
- 1,028 (64.3%) of the total 1,599 beneficiaries had a hospitalization within a 14-day period prior to initiating PPI therapy.

## CONCLUSIONS

Based on the analysis presented, there remains multiple opportunities for PPI deprescribing in MS Medicaid. During the study period, 34.2% of beneficiaries prescribed PPI therapy received them for > 90 days. Approximately 27.3% of beneficiaries receiving PPI therapy did not have a target diagnosis present in claims data. For beneficiaries with a diagnosis indicating short-term PPI therapy, 37.8% received > 90 days of PPI therapy. There also appears to be opportunities to encourage appropriate deprescribing of PPIs through transitions of care upon hospital discharge. Additionally, initial data did not indicate prescribers were switching beneficiaries to PPIs in the wake of drug recalls related to the H2 antagonist ranitidine.

## **RECOMMENDATIONS**

The DUR Board is asked to reaffirm the recommendations from the March 2018 DUR Board meeting or alter those recommendations.

*The recommendations from the March 2018 DUR Board meeting are below:*

- 1. DOM should set an electronic PA edit to limit the maximum days supply for PPI therapy to 90 days in a 12 month period before a PA is required.*
- 2. For therapy exceeding the 90 day limit, DOM should implement electronic or manual PA requirements for the maximum number of days supply based on diagnoses.*
- 3. MS-DUR should implement an educational initiative notifying providers of the new PPI prescribing criteria and guidance on deprescribing.*

## References:

1. Yamasaki T, Hemond C, Eisa M, Ganocy S, Fass R. The Changing Epidemiology of Gastroesophageal Reflux Disease: Are Patients Getting Younger? *J Neurogastroenterol Motil.* 2018;24(4):559-569. doi:10.5056/jnm18140
2. May D, Thiman M, Rao SSC. Gastroesophageal Reflux Disease. In: DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Ellingrod V, eds. *Pharmacotherapy: A Pathophysiologic Approach, 11e.* New York, NY: McGraw-Hill Education; 2020. [accesspharmacy.mhmedical.com/content.aspx?aid=1164173432](https://accesspharmacy.mhmedical.com/content.aspx?aid=1164173432). Accessed February 10, 2020.
3. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Ther Adv Gastroenterol.* 2012;5(4):219-232. doi:10.1177/1756283X12437358
4. Program Integrity: Proton Pump Inhibitor Education Materials. <https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/protonpump-education>. Accessed February 10, 2020.
5. Sandhu DS, Fass R. Current Trends in the Management of Gastroesophageal Reflux Disease. *Gut Liver.* 2018;12(1):7-16. doi:10.5009/gnl16615
6. Yadlapati R, Kahrilas PJ. When is proton pump inhibitor use appropriate? *BMC Med.* 2017;15. doi:10.1186/s12916-017-0804-x
7. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. *Ther Adv Drug Saf.* 2017;8(9):273-297. doi:10.1177/2042098617715381
8. University of Wyoming School of Pharmacy Laramie. Appropriate Use and Stewardship of Proton-Pump Inhibitors. <https://www.uspharmacist.com/article/appropriate-use-and-stewardship-of-protonpump-inhibitors>. Accessed February 14, 2020.
9. Vilcu A-M, Sabatte L, Blanchon T, et al. Association Between Acute Gastroenteritis and Continuous Use of Proton Pump Inhibitors During Winter Periods of Highest Circulation of Enteric Viruses. *JAMA Netw Open.* 2019;2(11):e1916205-e1916205. doi:10.1001/jamanetworkopen.2019.16205
10. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. *Am J Manag Care.* 2010;16(9):e228-234.
11. Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors. *Can Fam Physician.* 2017;63(5):354-364.
12. No Evidence of PPI Use Is Linked to Dementia or Alzheimer Disease. Pharmacy Times. <https://www.pharmacytimes.com/publications/issue/2018/march2018/no-evidence-of-ppi-use-is-linked-to-dementia-or-alzheimer-disease>. Accessed February 12, 2020.
13. Li M, Luo Z, Yu S, Tang Z. Proton pump inhibitor use and risk of dementia. *Medicine (Baltimore).* 2019;98(7). doi:10.1097/MD.00000000000014422
14. Faleck D, Salmasian H, Furuya Y, Larson E, Abrams J, Freedberg D. Proton Pump Inhibitors Do Not Increase Risk for Clostridium difficile Infection in the Intensive Care Unit. *Am J Gastroenterol.* 2016;111(11):1641-1648. doi:10.1038/ajg.2016.343
15. Lødrup AB, Reimer C, Bytzer P. Systematic review: symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. *Scand J Gastroenterol.* 2013;48(5):515-522. doi:10.3109/00365521.2012.746395
16. FDA: Testing Reveals Unacceptable Levels of NDMA in Two H2 Blockers. MPR. <https://www.empr.com/home/news/safety-alerts-and-recalls/fda-testing-reveals-unacceptable-levels-of-ndma-in-two-h2-blockers/>. Published November 4, 2019. Accessed February 10, 2020.
17. FDA Updates and Press Announcements on NDMA in Zantac (ranitidine). FDA. January 2020. <http://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine>. Accessed February 10, 2020.
18. Pittman, Eric. *Proton Pump Inhibitor and Potential Deprescribing Opportunities in MS Medicaid (2018)*. Mississippi Division of Medicaid; :49.
19. Omeprazole. <https://www.micromedexsolutions.com>.
20. Esomeprazole. <https://www.micromedexsolutions.com>.
21. Dexlansoprazole. <https://www.micromedexsolutions.com>.
22. Lansoprazole. <https://www.micromedexsolutions.com>.
23. Rabeprazole. <https://www.micromedexsolutions.com>.
24. Pantoprazole. <https://www.micromedexsolutions.com>.

25. Hall AJ, Rosenthal M, Gregoricus N, et al. Incidence of Acute Gastroenteritis and Role of Norovirus, Georgia, USA, 2004–2005 - Volume 17, Number 8—August 2011 - Emerging Infectious Diseases journal - CDC. doi:10.3201/eid1708.101533
26. Definition & Facts for Viral Gastroenteritis (“Stomach Flu”). National Institute of Diabetes and Digestive and Kidney Diseases. <https://www.niddk.nih.gov/health-information/digestive-diseases/viral-gastroenteritis/definition-facts>. Accessed February 14, 2020.
27. Mada PK, Alam MU. Clostridium Difficile. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2020. <http://www.ncbi.nlm.nih.gov/books/NBK431054/>. Accessed February 13, 2020.
28. Population Clock. US Census Bureau. <https://www.census.gov/popclock/>. Accessed February 13, 2020.