DUR Board Meeting
March 7, 2018
Heritage Center
Lecture Rooms A & B

north dakota
department of
human services

North Dakota Medicaid
DUR Board Meeting Agenda
Brynhild Haugland Room
State Capitol
600 East Boulevard Avenue
Bismarck, ND
March 7, 2018
1:00 pm

1. Administrative items
    - Travel vouchers

2. Old business
    - Review and approval of 12/17 meeting minutes
    - Budget update
    - Review top 15 therapeutic categories/top 25 drugs
    - Prior authorization/PDL update
    - Second review of Skelaxin
    - Second review of Eucrisa
    - Review of first fill of narcotics

3. New business
    - Review of Anzemet and Zuplenz
    - Review of biosimilar agents
    - Review of Dupixent
    - Review of Duzallo
    - Review of Gocovri
    - Review of Tussicaps
    - Review of topical corticosteroid agents
    - Review of codeine and tramadol utilization
    - Review of Adderall utilization
    - Review of Proton Pump Inhibitor utilization
    - Criteria recommendations
    - Upcoming meeting date/agenda. Next meeting is June 6, 2018 in the Sakakawea Room

4. Adjourn

Please remember to silence all cellular phones during the meeting.

Drug Utilization Review (DUR) Meeting Minutes

December 6, 2017

Members Present: Wendy Brown, Tanya Schmidt, Laura Schield, Michael Quast, Zach Marty, LeNeika Roehrich, Andrea Honeyman, Carlotta McCleary, Peter Woodrow, Michael Booth

Members Absent: Gaylord Kavlie, Katie Kram, Jeffrey Hostetter, Russ Sobotta

Medicaid Pharmacy Department: Brendan Joyce, Alexi Murphy, Gary Betting

Old Business

Chair W. Brown called the meeting to order at 1:04 p.m. Chair W. Brown asked for a motion to approve the minutes of the September meeting. T. Schmidt moved that the minutes be approved and A. Honeyman seconded the motion. Chair W. Brown called for a voice vote to approve the minutes. The motion passed with no audible dissent.

Announcements

A. Murphy informed the board of new functionalities in the MMIS claims system that allow for a diagnosis field to be used during claims processing, as well as the ability for the system to automatically scan for concurrent medications. The board was informed that these new functionalities have since been utilized to create edits to check for diagnoses and/or concurrent medications for a select few medication classes such as stimulants and SGLT-2 inhibitors. The board was further informed that additional edits will be implemented in the future for medications on the Preferred Drug List that only require concurrent therapy and/or FDA approved diagnoses. A. Murphy also informed the board that a class review of topical corticosteroids would be presented at the next DUR board meeting to later designate prior authorization criteria for this class of medications.

Review Top 15 Therapeutic Categories/Top 25 Drugs

B. Joyce presented the quarterly review of the top 15 therapeutic classes by total cost of claims, top 25 drugs based on number of claims, and top 25 drugs based on claims cost for the 3rd quarter of 2017.

PDL Update

A. Murphy shared with the Board all of changes made to the Preferred Drug List since the most recent 2017 version of the Preferred Drug List was posted. A total of twenty-one medications were added to the list of PDL medications requiring prior authorization and Moviprep will no longer require prior authorization. Kymriah, Parsabiv, Renflexis, and Xiaflex were added to the Medical Billing Only list of medications.

Annual Review of Prior Authorization Forms and Criteria

The Board reviewed all forms and criteria utilized for all medications that are currently placed on prior authorization. L. Schield spoke to difficulties with navigating the website used to house the forms, criteria, and Preferred Drug List. T. DeRuiter and A. Murphy agreed to provide consolidated,

searchable criteria and review potential ways the website can be restructured to simplify navigation. No changes were recommended during the review of the forms and criteria.

New Business

Discussion on Opioid and Benzodiazepine Abuse and Overdose Diagnoses

A. Murphy and B. Joyce presented statistics on opioid, benzo, heroin, and other psychotropic drug overdoses in the North Dakota Medicaid population during 2017. A. Murphy and B. Joyce presented recommended claims processing edits that could be put into place to try to reduce overdoses of benzodiazepines and opioids in the North Dakota Medicaid population, as well as a step-wise approach in which the edits could be implemented. The board agreed that the presented edits would be beneficial.

Emflaza

B. Joyce briefly discussed Emflaza with the board for the purpose of removing it from the PA criteria for medications >$3,000 to have its own separate criteria. A motion was made by P. Woodrow to manage the medication separately through prior authorization. The motion was seconded by L. Schield.

Skelaxin

T. DeRuiter and B. Joyce reviewed Skelaxin with the Board. A motion was made by M. Booth to manage the medication through prior authorization. The motion was seconded by P. Woodrow. This topic will be reviewed at the next meeting

Eucrisa

T. DeRuiter and B. Joyce reviewed Eucrisa with the Board. A motion was made by M. Quast to manage the medication through prior authorization. The motion was seconded by L. Roehrich. This topic will be reviewed at the next meeting

Criteria Recommendations

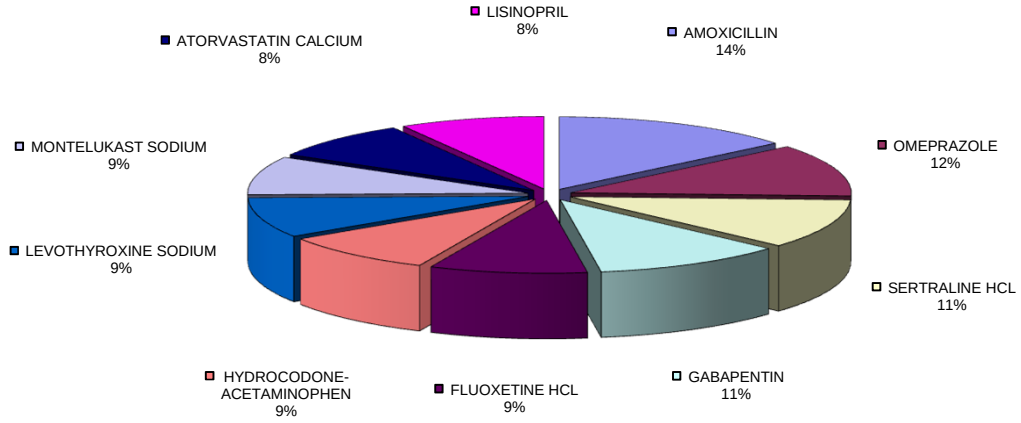
The recommended RDUR criteria enclosed in the packet were developed from product information provided by the manufacturers and are usually consistent with new indications, new drugs added, and new warnings. These proposed criteria will be added to the current set of criteria and will be used in future DUR cycles. L. Roehrich moved to approve the new criteria and T. Schmidt seconded the motion. The motion passed with no audible dissent. The next DUR Board meeting will be held March 7, 2018 at the Capitol in the Brynhild Haugland room in Bismarck. W. Brown adjourned the meeting.

TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 10/01/2017 - 12/31/2017

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
AMOXICILLIN	PENICILLINS	3,341	$ 114,852.65	$ 34.38	2.22%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	2,779	$ 53,085.31	$ 19.10	1.85%
SERTRALINE HCL	ANTIDEPRESSANTS	2,619	$ 49,560.47	$ 18.92	1.74%
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	2,612	$ 80,446.91	$ 30.80	1.74%
FLUOXETINE HCL	ANTIDEPRESSANTS	2,162	$ 37,299.26	$ 17.25	1.44%
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	2,141	$ 60,531.33	$ 28.27	1.43%
LEVOTHYROXINE SODIUM	THYROID AGENTS	2,124	$ 42,517.45	$ 20.02	1.41%
MONTELUKAST SODIUM	LEUKOTRIENE MODIFIERS	2,036	$ 35,908.21	$ 17.64	1.36%
ATORVASTATIN CALCIUM	HMG-COA REDUCTASE INHIBITORS	2,005	$ 53,508.41	$ 26.69	1.33%
LISINOPRIL	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS	1,992	$ 41,411.53	$ 20.79	1.33%
TRAZODONE HCL	ANTIDEPRESSANTS	1,891	$ 28,147.94	$ 14.89	1.26%
METHYLPHENIDATE ER	RESPIRATORY AND CNS STIMULANTS	1,806	$ 337,902.25	$ 187.10	1.20%
AZITHROMYCIN	MACROLIDES	1,645	$ 40,607.29	$ 24.69	1.09%
CLONIDINE HCL	CENTRAL ALPHA-AGONISTS	1,638	$ 28,606.08	$ 17.46	1.09%
VYVANSE	AMPHETAMINES	1,549	$ 320,058.64	$ 206.62	1.03%
ESCITALOPRAM OXALATE	ANTIDEPRESSANTS	1,514	$ 28,020.71	$ 18.51	1.01%
METFORMIN HCL	BIGUANIDES	1,506	$ 24,192.11	$ 16.06	1.00%
PROAIR HFA	BETA-ADRENERGIC AGONISTS	1,457	$ 110,467.65	$ 75.82	0.97%
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	1,433	$ 57,900.01	$ 40.40	0.95%
AMOXICILLIN-CLAVULANATE POTASS	PENICILLINS	1,401	$ 49,903.02	$ 35.62	0.93%
BUPROPION XL	ANTIDEPRESSANTS	1,382	$ 33,022.56	$ 23.89	0.92%
RISPERIDONE	ANTIPSYCHOTIC AGENTS	1,365	$ 19,946.47	$ 14.61	0.91%
QUETIAPINE FUMARATE	ANTIPSYCHOTIC AGENTS	1,328	$ 23,806.33	$ 17.93	0.88%
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	1,309	$ 50,581.30	$ 38.64	0.87%
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	1,268	$ 27,050.53	$ 21.33	0.84%
TOTAL TOP 25		46,303	$ 1,749,334.42	$ 37.78	30.82%

Total Rx Claims From 10/01/2017 - 12/31/2017	150,244

Top 10 Drugs
Based on Number of Claims

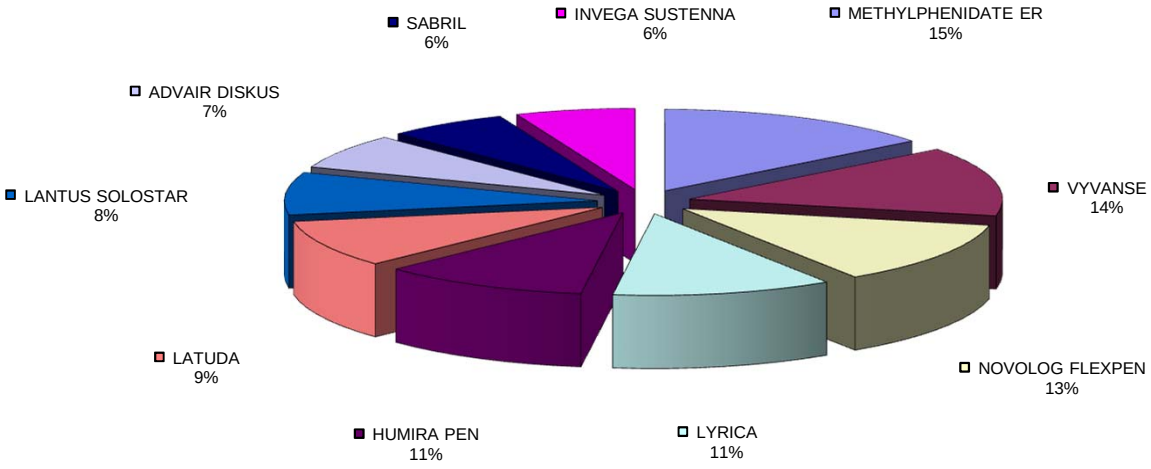


TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 10/01/2017 - 12/31/2017

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
METHYLPHENIDATE ER	RESPIRATORY AND CNS STIMULANTS	1,806	$ 337,902.25	$ 187.10	1.20%
VYVANSE	AMPHETAMINES	1,549	$ 320,058.64	$ 206.62	1.03%
NOVOLOG FLEXPEN	INSULINS	570	$ 290,514.63	$ 509.67	0.38%
LYRICA	ANTICONVULSANTS, MISCELLANEOUS	625	$ 264,636.83	$ 423.42	0.42%
HUMIRA PEN	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	56	$ 249,889.77	$ 4,462.32	0.04%
LATUDA	ANTIPSYCHOTIC AGENTS	305	$ 217,323.81	$ 712.54	0.20%
LANTUS SOLOSTAR	INSULINS	505	$ 196,161.64	$ 388.44	0.34%
ADVAIR DISKUS	CORTICOSTEROIDS (RESPIRATORY TRACT)	502	$ 161,082.55	$ 320.88	0.33%
SABRIL	ANTICONVULSANTS, MISCELLANEOUS	8	$ 145,563.63	$ 18,195.45	0.01%
INVEGA SUSTENNA	ANTIPSYCHOTIC AGENTS	82	$ 143,894.77	$ 1,754.81	0.05%
VIMPAT	ANTICONVULSANTS, MISCELLANEOUS	210	$ 121,908.15	$ 580.52	0.14%
AMOXICILLIN	PENICILLINS	3,341	$ 114,852.65	$ 34.38	2.22%
NORDITROPIN FLEXPRO	PITUITARY	31	$ 113,280.07	$ 3,654.20	0.02%
PROAIR HFA	BETA-ADRENERGIC AGONISTS	1,457	$ 110,467.65	$ 75.82	0.97%
ONFI	BENZODIAZEPINES (ANTICONVULSANTS)	104	$ 110,391.06	$ 1,061.45	0.07%
LEVEMIR FLEXTOUCH	INSULINS	365	$ 109,925.83	$ 301.17	0.24%
LICE KILLING	SCABICIDES AND PEDICULICIDES	282	$ 109,089.00	$ 386.84	0.19%
ADDERALL XR	AMPHETAMINES	587	$ 108,621.40	$ 185.04	0.39%
GILENYA	IMMUNOMODULATORY AGENTS	14	$ 99,725.15	$ 7,123.23	0.01%
NIX	SCABICIDES AND PEDICULICIDES	274	$ 97,691.44	$ 356.54	0.18%
SYMBICORT	CORTICOSTEROIDS (RESPIRATORY TRACT)	340	$ 96,782.40	$ 284.65	0.23%
COPAXONE	IMMUNOMODULATORY AGENTS	14	$ 95,839.36	$ 6,845.67	0.01%
SPIRIVA	ANTIMUSCARINICS/ANTISPASMODICS	300	$ 93,240.17	$ 310.80	0.20%
FOCALIN XR	RESPIRATORY AND CNS STIMULANTS	282	$ 83,312.02	$ 295.43	0.19%
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	2,612	$ 80,446.91	$ 30.80	1.74%
TOTAL TOP 25		16,221	$ 3,872,601.78	$ 238.74	10.80%

Total Rx Claims From 10/01/2017 - 12/31/2017	150,244

Top 10 Drugs
Based on Total Claims Cost



Prior Authorization/PDL Update

Criteria update
Hepatitis C

Added to PA	Category
DUZALLO	antihyperuricemic
NITYR	>3000
XHANCE	nasal steroid
PREVYMIS	>3000
OZEMPIC	GLP-1
XIMINO	Acne
BYDUREON BCISE	GLP-1 Agonist
QTERN	DPP-4 Inhibitor/SGLT2 Inhibtor
TRACLEER	Pulmonary Hypertension
REBINYN	Antihemophilia
HEMLIBRA	Antihemophilia
BEVYXXA	Oral Anticoagulant
ADMELOG	Insulin
ADMELOG SOLOSTAR	Insulin
STEGLATRO	SGLT2 Inhibtor
STEGLUJAN	DPP-4 Inhibitor/SGLT2 Inhibtor
ODACTRA	Allergenic Extracts
TOLMETIN SODIUM	NSAIDs
PIROXICAM	NSAIDs
ETODOLAC	NSAIDs
ETODOLAC ER	NSAIDs
DICLOFENAC SODIUM	NSAIDs
DICLOFENAC SODIUM ER	NSAIDs
DICLOFENAC POTASSIUM	NSAIDs
SUBLOCADE	buprenorphine

Removed from PA	Category
Naltrexone	Naltrexone
Alteplase	Alteplase
Pradaxa	Oral Anticoagulants
Xarelto	Oral Anticoagulants
Eliquis	Oral Anticoagulants
Savaysa	Oral Anticoagulants

Spiriva	COPD
Performoist	COPD
Anoro Ellilpta	COPD
Bevespi Aerosphere	COPD
Victoza	GLP-1 Agonists
Cosentyx	Immunomodulators
Enbrel	Immunomodulators
Humira	Immunomodulators
Androderm	Androgens
Androgel	Androgens
Adempas	PAH
Traceer	PAH
Orenitram ER	PAH
Ventavis 10 mg/ml	PAH
Pegasys	Hep C Interferon
Pegintron	Hep C Interferon
Sylatron	Hep C Interferon
Marinol	Dronabinol
Provigil	Provigil/Nuvigil
Arcalyst	>$3000
Benlysta	>$3000
Buphenyl	>$3000
Carbaglu	>$3000
Cerdelga	>$3000
Chenodal	>$3000
Cholbam	>$3000
Cuprimine	>$3000
Daraprim	>$3000
Esbriet	>$3000
Ilaris	>$3000
Keveyis	>$3000
Korlym	>$3000
Natpara	>$3000
Nityr	>$3000
Ocaliva	>$3000
Orfadin	>$3000
Orkambi	>$3000
Phenoxybenzamine Hcl	>$3000
Promacta	>$3000
Ravicti	>$3000

Samsca	>$3000
Somavert	>$3000
Strensiq	>$3000
Zavesca	>$3000

Bill Medical Side VIA 837I AND 837P TRANSACTIONS
ACTEMRA
ADASUVE
ARTISS
CINVANTI
FLOLAN
JETREA
KENGREAL
LEXTURNA
MEPSEVII
PREVYMIS
PROLASTIN C
QUTENZA
RADICAVA
SIMPONI ARIA
SOLIRIS
VARUBI
VELETRI
YESCARTA
ZILRETTA

North Dakota Department of Human Services
Skelaxin Prior Authorization Criteria

Initial and Renewal Requests: All requests are limited to a 3 month approval

- Patient must have had two 30-day trials of other skeletal muscle relaxants, one of which must be methocarbamol, as evidenced by paid claims or pharmacy print-outs.

health information designs

Skelaxin
Prior Authorization Form

Fax Completed Form to:
855-207-0250
For questions regarding this Prior authorization, call
866-773-0695

Prior Authorization Vendor for ND

ND Medicaid requires that patients receiving a new prescription for Skelaxin must meet the following criteria:

- **Patient must have had two 30-day trials of other skeletal muscle relaxants, one of which must be methocarbamol, as evidenced by paid claims or pharmacy print-outs.**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Prescriber Name	Specialist involved in therapy (if not treating physician)		
Prescriber NPI	Telephone Number	Fax Number	
Address	City	State	Zip Code

Requested Drug and Dosage: □ SKELAXIN	**Diagnosis for this request:**

List all failed medications:	**Start Date:**	**End Date:**

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Prescriber (or Staff) / Pharmacy Signature**	Date

**: *By completing this form, I hereby certify that the above request is true, accurate and complete. That the request is medically necessary, does not exceed the medical needs of the member, and is clinically supported in the patient's medical records. I also understand that any misrepresentations or concealment of any information requested in the prior authorization request may subject me to audit and recoupment.*

Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

North Dakota Department of Human Services
Eucrisa Prior Authorization Criteria

Initial Requests: Limited to 3 month approval

- Patient must have a diagnosis of a FDA-approved indication for use of Eucrisa
- Patient must have had a 6-week trial of at least one of the following, as evidenced by paid claims or pharmacy print-outs:
    - Tacrolimus or Pimecrolimus
- One of the following must be met (A or B):
    A. Patient must have had two 2-week trials of topical corticosteroids of medium or higher potency, as evidenced by paid claims or pharmacy print-outs.
    B. Patient must meet both of the following (1 and 2):
        1. Affected area is be on face, groin, axilla, or under occlusion OR patient is under 12 years of age
        2. Patient must have had two 2-week trials of topical corticosteroids of low or higher potency, as evidenced by paid claims or pharmacy print-outs.

Renewal Requests: Limited to 3 month approval

- Documentation from the prescriber must be provided showing that the patient has achieved a significant reduction in severity of atopic dermatitis.

health information designs

Eucrisa
Prior Authorization Form

Fax Completed Form to:
855-207-0250
For questions regarding this Prior authorization, call
866-773-0695

Prior Authorization Vendor for ND

ND Medicaid requires that patients receiving a new prescription for Eucrisa must meet the following criteria:

Initial Requests:

- Patient must have an FDA-approved diagnosis for use
- Patient must have had a 6-week trial of at least one of the following: Tacrolimus or Pimecrolimus
- One of the following must be met (A or B):
  - A. Patient must have had two 2-week trials of topical corticosteroids of medium or higher potency.
  - B. Patient must meet both of the following (1 and 2):
    1. Affected area is be on face, groin, axilla, or under occlusion OR patient is under 12 years of age
    2. Patient must have had two 2-week trials of topical corticosteroids of low or higher potency.

Renewal Requests:

- Documentation from the prescriber must be provided showing that the patient has achieved a significant reduction in severity of atopic dermatitis (please attach documentation to this request)

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Prescriber Name	Specialist involved in therapy (if not treating physician)		
Prescriber NPI	Telephone Number	Fax Number	
Address	City	State	Zip Code

Requested Drug: □ EUCRISA	**Diagnosis for this request:**	**Is the affected area is on the face, groin, axilla, or under occlusion?** □ YES □ NO

List all failed medications:	**Start Date:**	**End Date:**

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Prescriber (or Staff) / Pharmacy Signature**	Date

**: *By completing this form, I hereby certify that the above request is true, accurate and complete. That the request is medically necessary, does not exceed the medical needs of the member, and is clinically supported in the patient's medical records. I also understand that any misrepresentations or concealment of any information requested in the prior authorization request may subject me to audit and recoupment.*

Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

State	Lookback	Day Supply limit	Cumulative Limits	Limits on Rx	Exceptions
Arizona	60 days	5 days			cancer, hospice, palliative, end-of-life, children weaning post hospitalization, skilled nursing facility care, traumatic injury post surgical 14 days
Arkansas	60 days	7 days		50 MME/day	cancer
Colorado	365 days	7 days (for first 3 fills), 4th requires PA			Palliative care
Florida		7 days			excluding sickle cell, cancer, chronic non-malignant pain
Kansas		7 days, as of May 2018			
Missouri	90 days	7 days	60 days out of 90 days	50 MME/day (plan for March/April 18)	
Nevada	45 days	7 days	Total of 13 seven day prescriptions in rolling 12 month period	60 MME/day	cancer, post surgical with anticipated recovery longer than 3 months, palliative care, HIV/AIDS, residing in LTC facility, Rxs written by pain specialist
Ohio		7 days	no more than 14 days of therapy in rolling 45 d	60 MED/Rx	
Pennsylvania		3 days or more than 1 RX in 365 days for children 5 days or more than 1 RX in 180 days for adults		50 MME/day	excluding sickle cell, cancer, palliative care
Tennessee	180 days	5 days	After first fill, up to 10 additional days at 40 MME/day in each 180 day period	40MME/day	
Utah	60 days	7 days			
Virginia		7 days	2 seven day supplys in 60 day period	120 MME/day cumulative opioids	post op 14 days
Washington			Provider must attest to follow best practices for chronic use after 6 weeks	42 pills for 21 and older 18 pills for 20 and younger	

PRODUCT DETAILS OF Anzemet (dolasetron)

INDICATIONS AND USE:

- Anzemet is a selective serotonin receptor (5-HT3) antagonist, indicated for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in adults and children 2 years and older

DOSAGE AND ADMINISTRATION:

- Max dose is 100 mg
    - Adult Dosing:
        - 100 mg given within 1 hour before chemotherapy
    - Pediatric Dosing:
        - 1.8 mg/kg given within 1 hour before chemotherapy

DOSAGE FORM AND STRENGTHS:

- 50 and 100 mg tablets

CONTRAINDICATIONS:

- Hypersensitivity to dolasetron or any component of the formulation

WARNINGS AND PRECAUTIONS:

- Dose-dependent QT interval prolongation: Avoid in patients with congenital long QT syndrome, hypomagnesemia, or hypokalemia. Hypokalemia and hypomagnesemia must be corrected prior to administration.
- **Dose-dependent PR and QRS interval prolongation**: Patients with underlying structural heart disease and preexisting conduction system abnormalities or patients receiving drugs known to prolong the PR interval and QRS interval at high risk. Avoid in patients with complete heart block or at risk for complete heart block, unless they have an implanted pacemaker.
- Serotonin syndrome: 5-HT3 receptor antagonists are known to cause serotonin syndrome, particularly when used in combination with other serotonergic agents.

ADVERSE REACTIONS:

- Headache (18-23%)
- Cardiovascular: Bradycardia (4% to 5%), tachycardia (≤3%)
- Central nervous system: Fatigue (3-6%), dizziness (1-6%), pain (≤3%)
- Gastrointestinal: Diarrhea (2-5%), dyspepsia (≤3%)

DRUG INTERACTIONS

- Drugs that prolong the QTc interval (e.g. quetiapine, clozapine, amitriptyline, doxepin)
- Serotonergic modulators (e.g. SSRIs, SNRIs, tramadol, TCAs, Triptans).

COST

Drug	Strength	Package Size	WAC Pkg Price	AWP Unit Price
Anzemet Tablet	50 mg	5 tabs	360.27	86.46
Anzemet Tablet	100 mg	5 tabs	477.53	114.61
Anzemet IV sln	20 mg/1 ml	6s (0.625 mL)	140.89	45.09
Anzemet IV sln	20 mg/1 ml	25 mL	293.13	14.07
Anzemet IV sln	20 mg/1 ml	5 mL	58.63	14.07

CURRENT UTILIZATION

ND Medicaid Anzemet Utilization (10/2017 – 12/2017)		
Label Name	**Rx Num**	**Total Reimb Amt**
ANZEMET	0	N/A

REFERENCES:

1. Facts & Comparisons eAnswers. Available at http://online.factsandcomparisons.com. Accessed on February 10. 2018.
2. Anzemet (dolasetron) tablets [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; June 2016.

OVERVIEW OF BIOSIMILAR PRODUCTS

BIOSIMILAR DEFINITION

- The biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components
    - Extensively analyzing the structure and function of both the reference product and the proposed biosimilar (purity, chemical identity, and bioactivity)
    - Minor differences between the reference product and the proposed biosimilar product in clinically inactive components are acceptable
- There are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.
    - Generally demonstrated through human and animal pharmacokinetic and pharmacodynamic studies, an assessment of clinical immunogenicity, and (if needed) additional clinical studies

Biosimilar Approval	Biosimilar Product	Original Product	Available
03/06/15	Zarxio (filgrastim-sndz)	Neupogen (filgrastim)	Yes
04/05/2016	Inflectra (infliximab-dyyb)	Remicade (infliximab)	Yes
08/30/2016	Erelzi (etanercept-szzs)	Enbrel (etanercept)	No
09/23/2016	Amjevita (adalimumab-atto)	Humira (adalimumab)	No
04/21/2017	Renflexis (infliximab-abda)	Remicade (infliximab)	Yes
08/25/2017	Cyltezo (adalimumab-adbm)	Humira (adalimumab)	No
09/14/2017	Mvasi (bevacizumab-awwb)	Avastin (bevacizumab)	No
12/01/2017	Ogivri (trastuzumab-dkst)	Herceptin (trastuzumab)	No
12/13/2017	Ixifi (infliximab-qbtx)	Remicade (infliximab)	No

DIFFERENCES BETWEEN REFERENCE AND BIOSIMILAR & INTERCHANGABILITY

- Currently, no biosimilar products are deemed as “interchangeable” with their reference product
- An interchangeable product is a biosimilar product that meets additional requirements outlined by the Biologics Price Competition and Innovation Act
    - Must show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient
    - For products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product will have been evaluated
    - An interchangeable product may be substituted for the reference product without the involvement of the prescriber
- Biosimilar agents do not necessarily carry all of the same FDA indications as their reference product
    - Sometimes have small but potentially significant differences in the wording of their indications compared to their reference product

Biosimilar	Original	Differences
Zarxio	Neupogen	Acute hematopoietic radiation injury syndrome (Neupogen only) Myelosuppressive chemotherapy recipients with nonmyeloid malignancies: • decrease the duration of severe neutropenia (Zarxio) • decrease the incidence of infection (Neupogen)
Inflectra, Ixifi, & Renflexis	Remicade	Ulcerative Colitis (Remicade only)
Erelzi	Enbrel	Treatment of patients 4 years and older (Enbrel) or 18 years and older (Erelzi) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Amjevita & Cyltezo	Humira	Hidradenitis suppurativa (Humira only) Uveitis (Humira only)
Mvasi	Avastin	Glioblastoma, progressive (Mvasi) vs. Glioblastoma, recurrent (Avastin) Ovarian (epithelial), fallopian tube, or primary peritoneal cancer (Avastin only)

CURRENT UTILIZATION

ND Medicaid Biosimilar Utilization (10/2017-12/2017)		
Label Name	**Rx Num**	**Total Reimb Amt**
Zarxio	1	$2,769.06

REFERENCES:

1. Facts & Comparisons eAnswers. Available at http://online.factsandcomparisons.com. Accessed on February 10, 2018.
2. Cyltezo (adalimumab) [prescribing information]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals Inc: August 2017.
3. Erelzi (etanercept) [prescribing information]. Princeton, NJ: Sandoz Inc; August 2016.
4. Inflectra (infliximab dyyb) [prescribing information]. New York, NY: Pfizer; November 2017.
5. Ixifi (infliximab-qbtx) [prescribing information]. New York, NY: Pfizer; December 2017.
6. Renflexis (infliximab) [prescribing information]. Kenilworth, NJ: Merck Sharp & Dohme; April 2017.
7. Granix (tbo-filgrastim) [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; June 2017.
8. Amjevita (adalimumab-atto) [prescribing information]. Thousand Oaks, CA: Amgen Inc; September 2016.
9. Mvasi (bevacizumab-awwb) [prescribing information]. Thousand Oaks, CA: Amgen Inc; September 2017.

PRODUCT DETAILS OF Dupixent (dupilumab)

INDICATIONS AND USE:

- Moderate to severe atopic dermatitis, not adequately controlled with topical therapies or when those therapies are inadvisable.
- Orphan drug designation: Treatment of short bowel syndrome

DOSAGE AND ADMINISTRATION:

- Adults
  - Initial: 600 mg subQ, divided in 2 different injection sites
  - Maintenance: 300 mg subQ every other week
- Pediatric
  - Safety and effectiveness have not been established

DOSAGE FORM AND STRENGTHS:

- 300 mg/2 mL prefilled syringe

CONTRAINDICATIONS:

- Hypersensitivity to the product or any component of the formulation

WARNINGS AND PRECAUTIONS:

- **Ocular effects**: Conjunctivitis and keratitis have been reported; report new onset or worsening eye symptoms to health care provider
- **Asthma**: Safety and efficacy have not been established in the treatment of asthma. Discontinuation or adjustment of asthma medications in patients with comorbid asthma should not be done without consulting health care provider
- **Appropriate use:** May be used in combination with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only (eg, face, neck intertriginous and genital areas)
- **Immunogenicity**: Dupilumab antibodies, including neutralizing antibodies, may develop (may be associated with lower serum dupilumab concentrations)

ADVERSE REACTIONS:

- Dermatologic: Herpes simplex infection (2%)
- Gastrointestinal: Oral herpes (4%)
- Immunologic: Antibody development (7%; neutralizing: 2%)
- Injection site reaction (10%)
- Ophthalmic: Conjunctivitis (10%), eye pruritus (1%)

DRUG INTERACTIONS

- Live Vaccines

COST

Drug	Strength	Package Size	WAC Pkg Price	AWP Unit Price
Dupixent sln	300 mg/2 ml	2 syr (2 mL)	2846.16	853.84750

CURRENT UTILIZATION

ND Medicaid Dupixent Utilization (10/2017 – 12/2017)		
Label Name	**Rx Num**	**Total Reimb Amt**
DUPIXENT	0	N/A

REFERENCES:

1. Facts & Comparisons eAnswers. Available at http://online.factsandcomparisons.com. Accessed on February 10, 2018.
2. Dupixent (dupilumab) [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals; March 2017.

PRODUCT DETAILS OF DUZALLO (lesinurad/allopurinol)

INDICATIONS AND USE:

- Treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a medically appropriate daily dose of allopurinol alone.

DOSAGE AND ADMINISTRATION:

- Max dose of lesinurad is 200 mg once daily
- Recommended dosing
    - ADULTS:
        - 1 tablet daily at an allopurinol dose equivalent to patient's current dose
    - PEDIATRIC:
        - Safety and efficacy have not been established

DOSAGE FORM AND STRENGTHS:

- lesinurad/allopurinol 200/200 mg and 200/300 mg tablets

CONTRAINDICATIONS:

- Hypersensitivity to the product or any component of the formulation
- Severe renal impairment (CrCl <30 mL/minute), ESRD, kidney transplant recipients, dialysis
- Tumor lysis syndrome
- Lesch-Nyhan syndrome

WARNINGS AND PRECAUTIONS:

- **Renal Impairment:** Lesinurad, when used concurrently with a xanthine oxidase inhibitor, is associated with an increased incidence of serum creatinine elevations and may cause renal failure or nephrolithiasis. Contraindicated if CrCl <30 mL/min and should be avoided if CrCl is <45 mL/min.
- **Cardiovascular events:** Major cardiac adverse events (cardiovascular deaths, nonfatal MI, or nonfatal strokes) were observed in clinical trials.
- **Secondary hyperuricemia:** Lesinurad has not been studied in patients with secondary hyperuricemia.
- **Gout flare:** Following initiation therapy. Use gout flare prophylaxis when initiating treatment.
- **CYP2C9 poor metabolizers:** Use with caution in CYP2C9 poor metabolizers and patients taking concomitant moderate CYP2C9 inhibitors.
- **Hepatotoxicity:** Cases of reversible hepatotoxicity (allopurinol). Asymptomatic elevations of serum alkaline phosphatase or AST and ALT have been observed.
- **Bone marrow suppression:** Bone marrow suppression (allopurinol)

ADVERSE REACTIONS:

- Increased serum creatinine (6%), ALT/AST increases
- Headache (5%)
- GERD (3%)
- Hypersensitivity (~3% rash, discontinue immediately)
- Gout flare (6%)

DRUG INTERACTIONS

- Vitamin K antagonists
- Moderate CYP2C9 inhibitors: use with caution
- Mercaptopurine and azathioprine: will require dose reductions (1/3-1/4 normal dose)

COST

Drug	Strength	Package Size	WAC Pkg Price	AWP Unit Price
Duzallo Tablet	300-200 mg	30 tablets	371.00	14.84
Duzallo Tablet	200-200 mg	30 tablets	371.00	14.84

CURRENT UTILIZATION

ND Medicaid Duzallo Utilization (10/2017 – 12/2017)		
Label Name	**Rx Num**	**Total Reimb Amt**
DUZALLO	0	N/A

REFERENCES:

1. Facts & Comparisons eAnswers. Available at http://online.factsandcomparisons.com. Accessed on February 10, 2018.
2. Duzallo (lesinurad and allopurinol) [prescribing information]. Cambridge, MA: Ironwood Pharmaceuticals, Inc; November 2017.

PRODUCT DETAILS OF GOCOVRI (amantadine ER)

INDICATIONS AND USE:

- Treatment of dyskinesia in patients with Parkinson disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications.

DOSAGE AND ADMINISTRATION:

- Max dose of lesinurad is 200 mg once daily
- Recommended dosing
    - ADULTS:
        - 1 tablet daily at an allopurinol dose equivalent to what the patient is currently taking
    - PEDIATRIC:
        - Safety and efficacy have not been established

DOSAGE FORM AND STRENGTHS:

- 68.5 and 137 mg capsules

CONTRAINDICATIONS:

- Patients with ESRD

WARNINGS AND PRECAUTIONS:

- **Falling Asleep During Activities of Daily Living:** Advise patients prior to treatment; ordinarily discontinue if occurs.
- **Suicidality and Depression:** Monitor patients for depressed mood, depression, or suicidal ideation or behavior.
- **Hallucinations/Psychotic Behavior:** Patients with major psychotic disorder should ordinarily not be treated with GOCOVRI; observe patients for the occurrence of hallucinations throughout treatment, especially at initiation and after dose increases.
- **Dizziness and Orthostatic Hypotension:** Monitor patients for dizziness and orthostatic hypotension, especially after starting GOCOVRI or increasing the dose.
- **Withdrawal-Emergent Hyperpyrexia and Confusion:** Avoid sudden discontinuation.
- **Impulse Control/Compulsive Behaviors:** Ask patients about increased gambling urges, sexual urges, uncontrolled spending or other urges; consider dose reduction or discontinuation if occurs.

ADVERSE REACTIONS:

- Frequency of >10%
    - Hallucination, Dizziness
    - Dry mouth
    - Peripheral edema
    - Constipation
    - Fall, Orthostatic hypotension

DRUG INTERACTIONS

- **Other Anticholinergic Drugs:** Doses should be reduced if atropine-like effects occur.
- **Drugs Affecting Urinary pH:** Excretion increases with acidic urine; possible accumulation with urine change towards alkaline.
- **Live Attenuated Influenza Vaccines**: Not recommended during use.
- **Alcohol**: Concomitant use not recommended.

COST

Drug	Strength	Package Size	WAC Pkg Price	AWP Unit Price
Gocovri Caps	68.5 mg	60 caps	2375.00	47.50
Gocovri Caps	137 mg	60 caps	2375.00	47.50

CURRENT UTILIZATION

ND Medicaid Gocovri Utilization (10/2017 – 12/2017)		
Label Name	**Rx Num**	**Total Reimb Amt**
GOCOVRI	0	N/A

REFERENCES:

1. Facts & Comparisons eAnswers. Available at http://online.factsandcomparisons.com. Accessed on February 10, 2018.
2. Gocovri (amantadine hydrochloride extended-release) [prescribing information]. Emeryville, CA: Adams Pharma LLC; August 2017.

PRODUCT DETAILS OF TOPICAL CORTICOSTEROIDS

OVERVIEW

- Topical corticosteroids are anti-inflammatory agents approved for the treatment of inflammatory and pruritic manifestations of dermatoses.
    - Preferred in many cases to minimize systemic adverse events
- Classified based on their relative potency: very high (Class I), high (Class II), high-medium (Class III), medium (Class IV), medium-low (Class V), low (Class VI), and very-low (Class VII).
    - Very high potency agents: used to treat severe dermatoses over non-facial/intertriginous areas.
    - Medium to high potency agents: often used for the treatment of mild to moderate non-facial and non-intertriginous dermatoses.
    - Low to medium potency agents: used when large areas need to be treated
    - Low potency agents: used on the eyelids and genital areas.

Topical Corticosteroid Potency Classification			
	Drug	**Formulation**	**Strength**
Very High Potency	augmented betamethasone dipropionate (Diprolene)	Ointment Lotion Gel	0.05%
	clobetasol propionate (Clobex, Cormax, Temovate/E, Olux/E)	Lotion Shampoo Spray Cream Gel Ointment Solution Foam	0.05%
	fluocinonide (Vanos)	Cream	0.1%
	flurandrenolide (Cordran)	Tape	4mcg/cm^2
	halobetasol propionate (Ultravate)	Ointment Cream	0.05%
High Potency	amcinonide (Cyclocort)	Ointment	0.1%
	augmented betamethasone dipropionate (Diprolene AF)	Cream	0.05%
	betamethasone dipropionate (Diprolene)	Ointment	0.05%
	desoximetasone (Topicort, Topicort LP)	Ointment Cream Gel	Ointment: 0.25% Cream: 0.25% Gel: 0.05%
	diflorasone diacetate (ApexiCon E, Psorcon)	Ointment	0.05%
	fluocinonide (Lidex/E)	Ointment Gel Cream Solution	0.05%
	halcinonide (Halog)	Ointment Cream	0.1%
	mometasone furoate (Elocon)	Ointment	0.1%
	triamcinolone acetonide (Trianex)	Ointment	0.5%

High-Medium Potency	amcinonide (Cyclocort)	Cream Lotion	0.1%
	betamethasone dipropionate (Diprolene)	Cream	0.05%
	betamethasone valerate (Valisone)	Ointment	0.1%
	diflorasone diacetate (ApexiCon E, Psorcon)	Cream	0.05%
	fluocinonide (Lidex/E)	Emollient Cream	0.05%
	fluticasone propionate (Cutivate)	Ointment	0.005%
	triamcinolone acetonide (Triderm)	Cream	0.5%
Medium Potency	betamethasone valerate (Luxiq)	Foam	0.12%
	clocortolone pivalate (Cloderm)	Cream	0.1%
	desoximetasone (Topicort)	Emollient Cream	0.05%
	fluocinolone acetonide (Synalar)	Ointment	0.025%
	flurandrenolide (Cordran)	Ointment	0.05%
	hydrocortisone valerate (Westcort)	Ointment	0.2%
	mometasone furoate (Elocon)	Cream Lotion Solution	0.1%
	prednicarbate (Dermatop)	Ointment	0.1%
	triamcinolone acetonide (Kenalog)	Ointment	0.1%
Medium-Low Potency	betamethasone dipropionate (Diprosone)	Lotion	0.05%
	betamethasone valerate (Valisone)	Cream Lotion	0.1%
	Desonide (DesOwen)	Ointment	0.05%
	fluocinolone acetonide (Synalar)	Cream	0.025%
	flurandrenolide (Cordran)	Cream Lotion Ointment	Cream/Lotion: 0.05% Ointment: 0.025%
	fluticasone proprionate (Cutivate)	Cream Lotion	0.05%
	hydrocortisone butyrate (Locoid/Lipocream, Cortizone 10)	Ointment Cream Lotion Solution	0.1%
	hydrocortisone probutate (Pandel)	Cream	0.1%
	hydrocortisone valerate (Westcort)	Cream	0.2%
	prednicarbate (Dermatop)	Cream	0.1%
	triamcinolone acetonide (Kenalog)	Lotion Ointment Cream	Cream/Lotion: 0.1% Ointment: 0.025%

Low Potency	alclometasone dipropionate (Aclovate)	Ointment Cream	0.05%
	desonide (Desonate, Desowen, Lokara, Verdeso)	Cream Gel Lotion Foam	0.05%
	fluocinolone acetonide (Capex Shampoo, Derma-Smoothe/FS)	Solution Shampoo Oil (Scalp) Oil (Body)	0.01%
	flurandrenolide (Cordran)	Cream	0.025%
	triamcinolone acetonide (Kenalog)	Cream Lotion	0.025%
Very Low Potency	hydrocortisone (Ala-Cort, Ala-Scalp, Nuzon, Scalacort, Scalacort-DK Kit, Texacort, Pediaderm HC, Pramosone, Analpram, Epifoam, Cortaid, Cortizone-10, Noble, Scalp Relief)	Ointment Cream Lotion Solution foam Spray	Ointment: 0.5%, 1%, or 2.5% Cream: 0.5%, 1%, or 2.5% Lotion: 1% or 2.5% Solution: 1% or 2.5% Aerosol foam: 1% Spray: 1%

PHARMACOLOGY

- Topical corticosteroids share anti-inflammatory, antipruritic, and vasoconstrictive actions that make them effective treatments in dermatological conditions. The exact mechanisms of action for the topical corticosteroids are not completely understood.

CONTRAINDICATIONS/WARNINGS

- HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, glucosuria, and growth retardation in children can result from the systemic absorption of topical corticosteroids. Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. If these effects are seen, the medications should be discontinued.

ADVERSE REACTIONS

- Local:
    - Burning; itching; irritation; erythema; dryness; folliculitis; hypertrichosis; pruritus; acneiform eruptions; hypopigmentation; perioral dermatitis; allergic contact dermatitis; numbness of fingers; stinging and cracking/tightening of skin; maceration of the skin; secondary infection; skin atrophy; striae; miliaria; telangiectasia. These may occur more frequently with occlusive dressings.
- Systemic:
    - Reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia and glycosuria.

ND Medicaid Utilization (10/2017 – 12/2017)			
Label Name	**Rx Num**	**Total Reimb Amt**	**Avg Cost per Script**
ALCLOMETASONE DIPR 0.05% OINT	2	$48.58	$24.29
ALCLOMETASONE DIPRO 0.05% CRM	1	$60.64	$60.64
BETAMETHASONE DP 0.05% CRM	18	$945.34	$52.52
BETAMETHASONE DP 0.05% LOT	4	$467.25	$116.81
BETAMETHASONE DP 0.05% OINT	7	$1,084.49	$154.93
BETAMETHASONE DP AUG 0.05% GEL	2	$122.26	$61.13
BETAMETHASONE VA 0.1% CREAM	4	$177.94	$44.49
BETAMETHASONE VA 0.1% LOTION	5	$610.20	$122.04
BETAMETHASONE VALER 0.1% OINTM	4	$107.19	$26.80
BETAMETHASONE VALER 0.12% FOAM	1	$442.13	$442.13
CAPEX SHAMPOO	2	$789.02	$394.51
CLOBETASOL 0.05% CREAM	16	$1,193.90	$74.62
CLOBETASOL 0.05% OINTMENT	27	$3,014.00	$111.63
CLOBETASOL 0.05% SHAMPOO	1	$202.37	$202.37
CLOBETASOL 0.05% SOLUTION	14	$861.72	$61.55
CLOBETASOL 0.05% TOPICAL LOTN	1	$195.93	$195.93
DESONIDE 0.05% CREAM	30	$2,972.41	$99.08
DESONIDE 0.05% LOTION	5	$748.60	$149.72
DESONIDE 0.05% OINTMENT	26	$3,180.95	$122.34
DESOXIMETASONE 0.05% GEL	1	$15.00	$15.00
DESOXIMETASONE 0.25% CREAM	2	$89.73	$44.87
FLUOCINOLONE 0.01% BODY OIL	23	$2,851.94	$124.00
FLUOCINOLONE 0.01% CREAM	1	$95.21	$95.21
FLUOCINOLONE 0.01% SOLUTION	3	$277.41	$92.47
FLUOCINOLONE 0.025% CREAM	1	$95.02	$95.02
FLUOCINOLONE 0.025% OINTMENT	3	$102.36	$34.12
FLUOCINOLONE OIL 0.01% EAR DRP	2	$301.76	$150.88
HALOBETASOL PROP 0.05% CREAM	1	$98.90	$98.90
HALOBETASOL PROP 0.05% OINTMNT	1	$57.12	$57.12
HYDROCORTISONE VAL 0.2% CREAM	4	$467.18	$116.80
HYDROCORTISONE VAL 0.2% OINTMT	14	$1,506.19	$107.59
MOMETASONE FUROATE 0.1% CREAM	16	$1,061.85	$66.37
MOMETASONE FUROATE 0.1% OINT	11	$217.97	$19.82
MOMETASONE FUROATE 50 MCG SPRY	2	$177.68	$88.84
TRIAMCINOLONE 0.025% CREAM	23	$302.99	$13.17
TRIAMCINOLONE 0.025% LOTION	2	$416.54	$208.27
TRIAMCINOLONE 0.025% OINT	20	$326.02	$16.30
TRIAMCINOLONE 0.1% CREAM	256	$4,833.86	$18.88
TRIAMCINOLONE 0.1% LOTION	12	$355.82	$29.65
TRIAMCINOLONE 0.1% OINTMENT	146	$2,239.92	$15.34

TRIAMCINOLONE 0.1% PASTE	9	$435.09	$48.34
TRIAMCINOLONE 0.147 MG/G SPRAY	1	$197.65	$197.65
TRIAMCINOLONE 0.5% CREAM	10	$156.52	$15.65
TRIAMCINOLONE 0.5% OINTMENT	13	$595.97	$45.84

REFERENCES:

1. Facts & Comparisons eAnswers. Available at http://online.factsandcomparisons.com. Accessed on February 10. 2018.
2. Bolognia JL, Jorizzo JL, Schaffer JV. Glucocorticosteroids. Dermatology. 3rd ed. 2012. Ch 125, 2075-88

PRODUCT DETAILS OF Tussicaps (hydrocodone polistirex/chlorpheniramine polistirex)

INDICATIONS AND USE:

- Treatment of cough associated with upper respiratory symptoms due to allergy or the common cold

DOSAGE AND ADMINISTRATION:

- Max dose is 2 capsules (20 mg hydrocodone & 16 mg chlorpheniramine) per day
- Recommended dosing
    - Adults and pediatrics 12 years of age and older:
        - 1 capsule (10 mg hydrocodone & 8 mg chlorpheniramine) every 12 hours
    - Pediatric patients 6 to 11 years of age:
        - 1 half-strength capsule (5 mg hydrocodone & 4 mg chlorpheniramine) every 12 hours

DOSAGE FORM AND STRENGTHS:

- hydrocodone-chlorpheniramine 5/4 mg and 10/8 mg capsules

CONTRAINDICATIONS:

- Hypersensitivity to the product or any component of the formulation
- Pediatric patients less than 6 years (increased risk of fatal respiratory depression)

WARNINGS AND PRECAUTIONS:

- Avoid use in patients with head trauma
- Use with caution in the following patients:
    - Patients with any of the following diagnoses/conditions: abdominal conditions, obstructive bowel disease, respiratory disease/depression, adrenocortical insufficiency, biliary tract impairment, delirium tremens, psychosis, seizures, thyroid dysfunction, obesity, and prostatic hyperplasia/urinary obstruction
    - Patients with severe renal or hepatic impairment
    - Elderly patients
    - Patients with a history of drug abuse or acute alcoholism
    - Cachectic or debilitated patients

ADVERSE REACTIONS:

- Frequency not defined
    - Anxiety, dizziness, drowsiness, dysphoria, euphoria, fear, impaired mental and physical performance, lethargy, mental clouding, mood change, psychic dependence, sedation.
    - Constipation, nausea, vomiting
    - Respiratory depression

DRUG INTERACTIONS

- Other CNS depressants (e.g. benzodiazepines, hypnotics, azelastine)
- Constipating agents (e.g. eluxadoline,
- CYP2D6 and CYP3A4 inhibitors
- CYP3A4 inducers
- Anticholinergic agents (e.g. umeclidinium, amantadine, glycopyrrolate)

COST

Drug	Strength	Package Size	WAC Pkg Price	AWP Unit Price
TussiCaps	4 mg-5 mg	100 caps	3641.43	43.70
TussiCaps	8 mg-10 mg	100 caps	3641.43	43.70
TussiCaps	4 mg-5 mg	20 caps	728.29	43.70
TussiCaps	8 mg-10 mg	20 caps	728.29	43.70

CURRENT UTILIZATION

ND Medicaid TussiCaps Utilization (10/2017-12/2017)		
Label Name	**Rx Num**	**Total Reimb Amt**
TUSSICAPS	0	N/A

REFERENCES:

1. Facts & Comparisons eAnswers. Available at http://online.factsandcomparisons.com. Accessed on February 10, 2018.
2. Product Information: TussiCaps(R) extended-release capsules, hydrocodone polistirex and chlorpheniramine polistirex extended-release capsules. Valeant Pharmaceuticals (per DailyMed), Bridgewater, NJ, 2014.

PRODUCT DETAILS OF Zuplenz (ondansetron)

INDICATIONS AND USE:

- Prevention of nausea and vomiting associated with moderate and highly emetogenic chemotherapy.
- Prevention of nausea and vomiting from radiotherapy in patients receiving total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen.
- Prevention of postoperative nausea and/or vomiting.

DOSAGE AND ADMINISTRATION:

- Max dose is 100 mg
    - Adult & Pediatric Patients 12 and Older Dosing:
        - 8 mg given twice daily
            - 1st dose 30 minutes prior to chemo, 2nd dose 8 hours later
            - Every 12 hours for 1-2 days after completion of chemo
    - Pediatric Dosing (ages 4 – 11 years): only for prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy
        - 4 mg film given three times a day
            - 1st dose 30 minutes prior to chemo, then 4 and 8 hours later
            - Every 8 hours for 1-2 days after completion of chemo

DOSAGE FORM AND STRENGTHS:

- 4 and 8 mg dissolving film

CONTRAINDICATIONS:

- Hypersensitivity to ondansetron or any component of the formulation
- Concomitant use of apomorphine

WARNINGS AND PRECAUTIONS:

- **Dose-dependent QT interval prolongation:** Avoid in patients with congenital long QT syndrome, hypomagnesemia, or hypokalemia. Hypokalemia and hypomagnesemia must be corrected prior to administration.
- **Serotonin syndrome:** 5-HT3 receptor antagonists are known to cause serotonin syndrome, particularly when used in combination with other serotonergic agents.

ADVERSE REACTIONS:

- Headache, malaise/fatigue, constipation, diarrhea

DRUG INTERACTIONS

- Drugs that prolong the QTc interval (e.g. quetiapine, clozapine, amitriptyline, doxepin)
- Serotonergic modulators (e.g. SSRIs, SNRIs, tramadol, TCAs, Triptans)
- Apomorphine: profound hypotension and loss of consciousness

COST

Drug	Strength	Package Size	WAC Pkg Price	AWP Unit Price
Zuplenz Film	4 mg	10 films	325.31	39.04
Zuplenz Film	8 mg	10 films	325.31	39.04
Zuplenz Film	4 mg	30 films	965.30	38.61
Zuplenz Film	8 mg	30 films	965.30	38.61

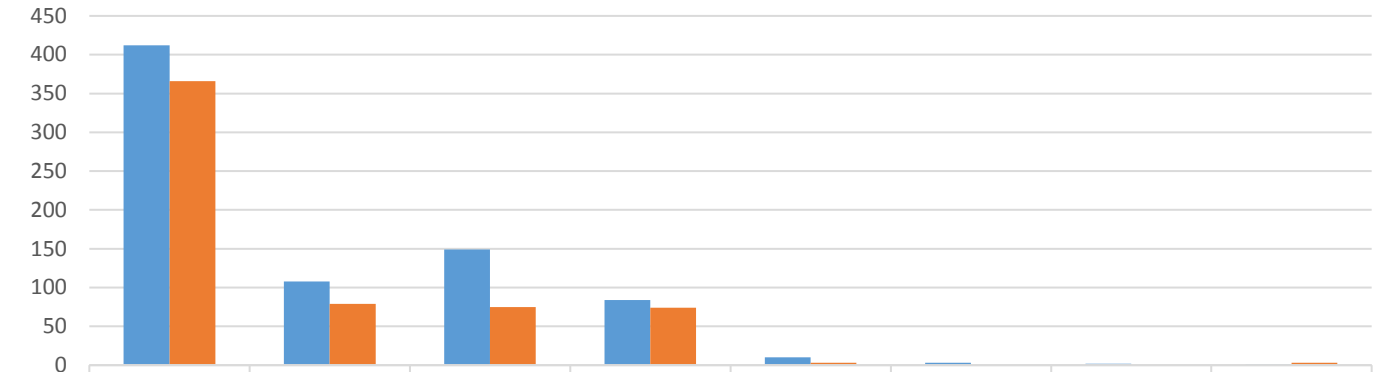
CURRENT UTILIZATION

ND Medicaid Zuplenz Utilization (10/2017-12/2017)		
Label Name	**Rx Num**	**Total Reimb Amt**
ZUPLENZ	0	N/A

REFERENCES:

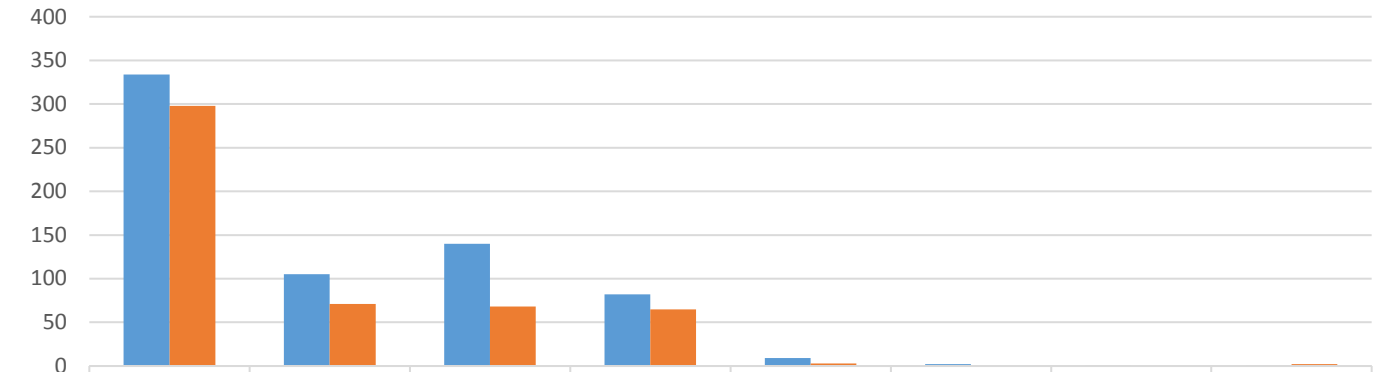
1. Facts & Comparisons eAnswers. Available at http://online.factsandcomparisons.com. Accessed on October 31, 2017.
2. Zuplenz oral soluble film (ondansetron) [prescribing information]. Raleigh, NC: Midatech Pharma US Inc.; January 2017.

Number of Claims per Month



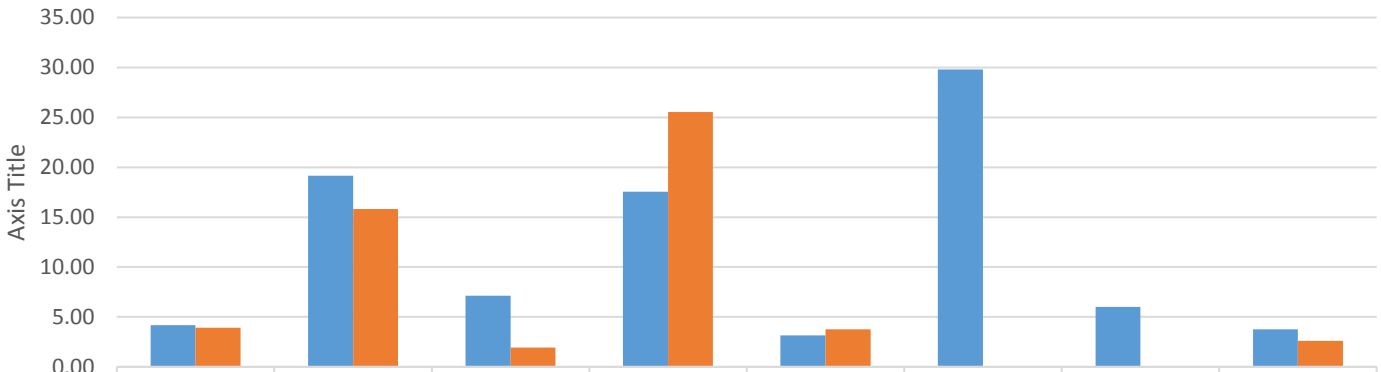
	TRAMADOL	PROMETH/ CODEINE	APAP/ CODEINE	CODEINE/ GUAIFENESIN	APAP/ TRAMADOL	PROMETH/ PHENYLEPH/ CODEINE	CODEINE SULFATE	BUTALBIT/ APAP/ CAFF/ CODEINE
2016	412	108	149	84	10	3	2	1
2017	366	79	75	74	3	0	0	3

Number of Patients per Month

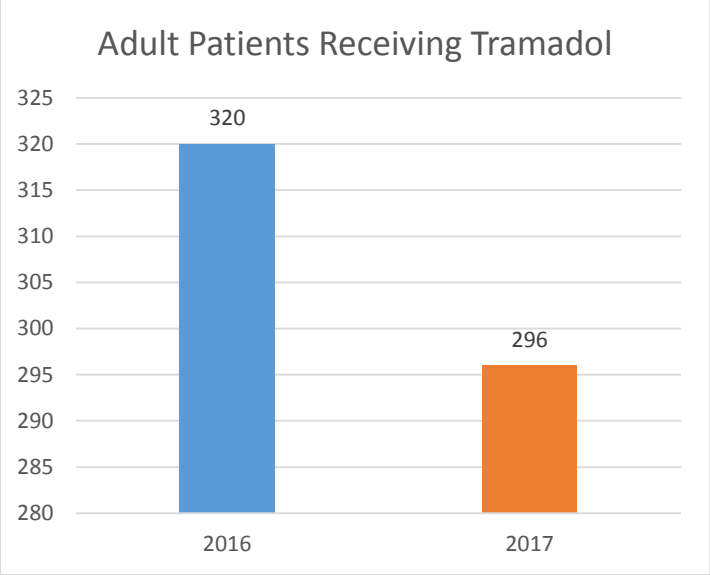


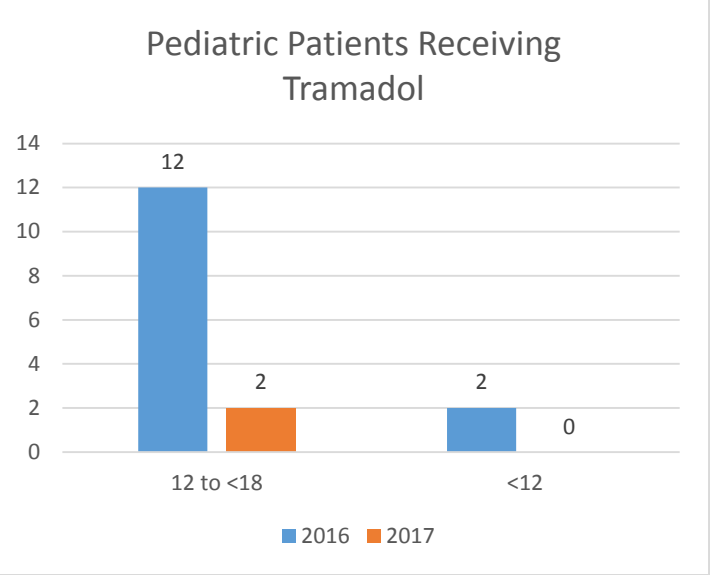
	TRAMADOL	PROMETH/ CODEINE	APAP/ CODEINE	CODEINE/ GUAIFENESIN	APAP/ TRAMADOL	PROMETH/ PHENYLEPH/ CODEINE	CODEINE SULFATE	BUTALBIT/ APAP/ CAFF/ CODEINE
2016	334	105	140	82	9	2	1	1
2017	298	71	68	65	3	0	0	2

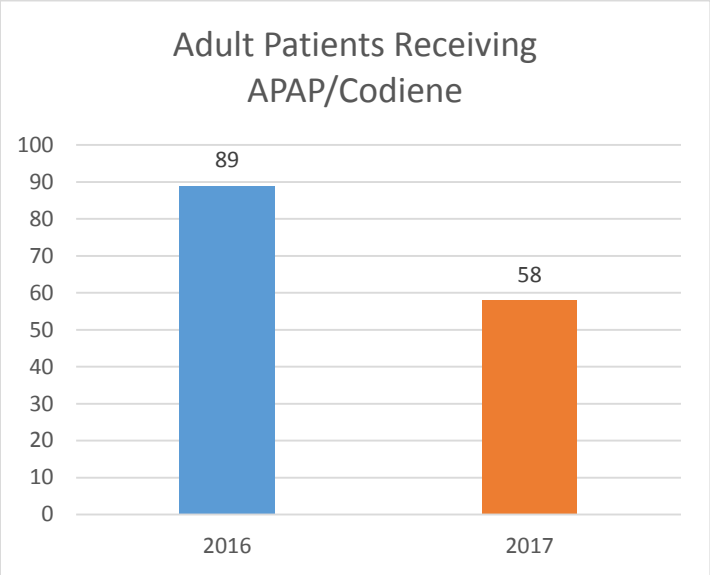
Quantity per Day of Each Product (mL, tablets, or capsules)

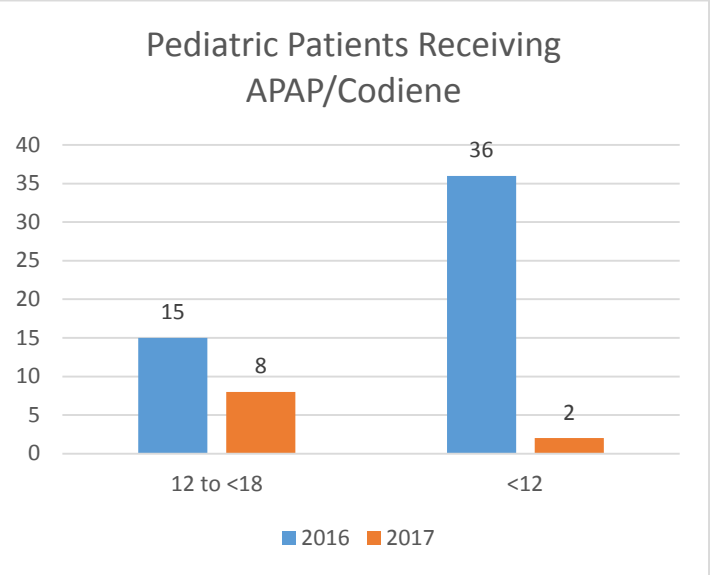


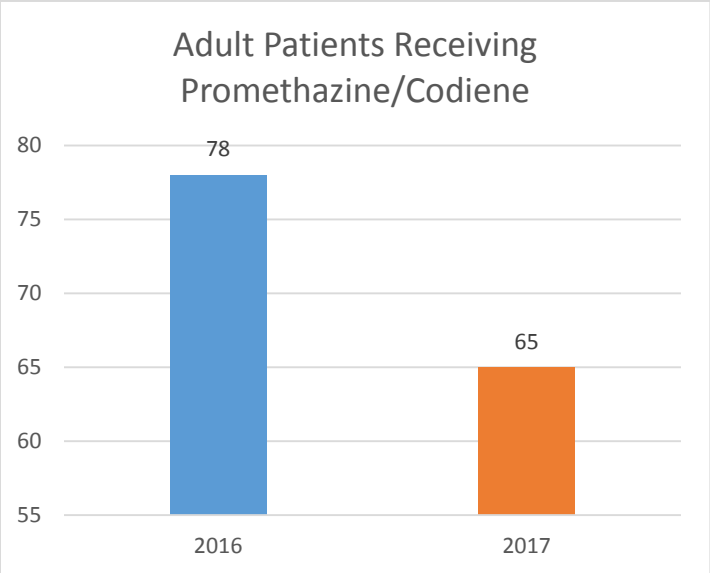
	TRAMADOL	PROMETH/ CODEINE	APAP/ CODEINE	CODEINE/ GUAIFENESIN	APAP/ TRAMADOL	PROMETH/ PHENYLEPH/ CODEINE	CODEINE SULFATE	BUTALBIT/ APAP/ CAFF/ CODEINE
2016	4.18	19.14	7.12	17.53	3.17	29.80	6.00	3.75
2017	3.91	15.81	1.94	25.53	3.75	0.00	0	2.61

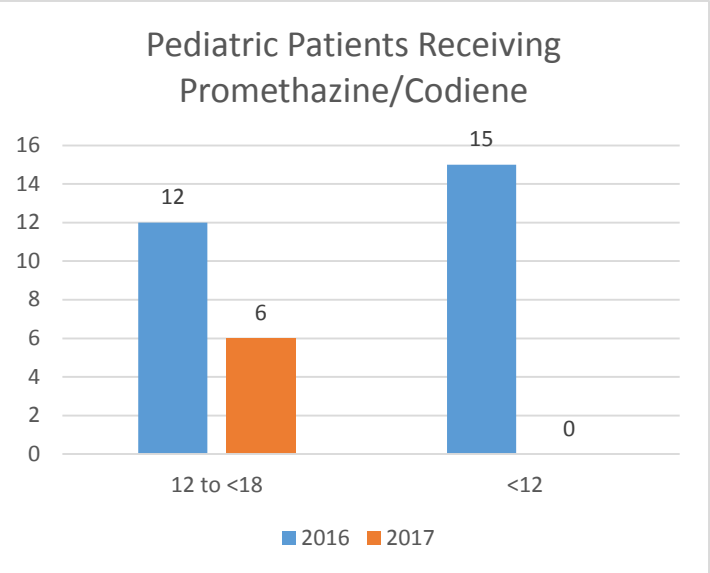

Adult Patients Receiving Tramadol
325
320
315
310
305
300
295
290
285
280
320
296
2016
2017

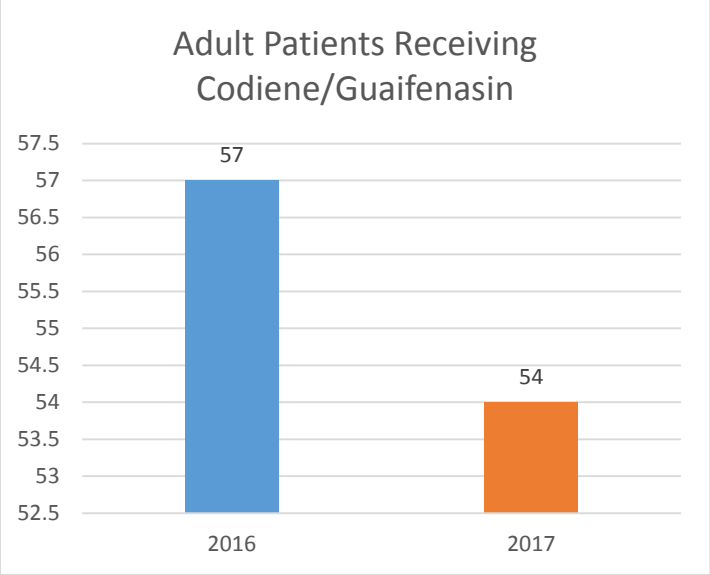

Pediatric Patients Receiving Tramadol
14
12
10
8
6
4
2
0
12
2
2
0
12 to <18
<12
2016
2017

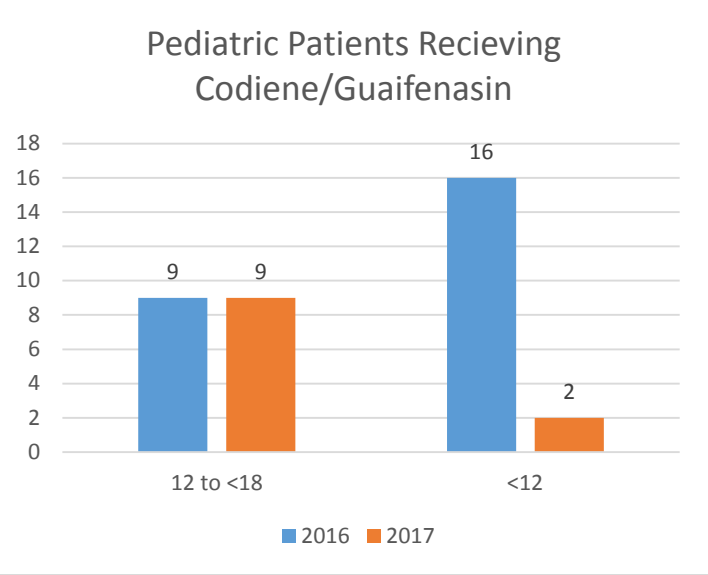

Adult Patients Receiving APAP/Codiene
100
90
80
70
60
50
40
30
20
10
0
89
58
2016
2017

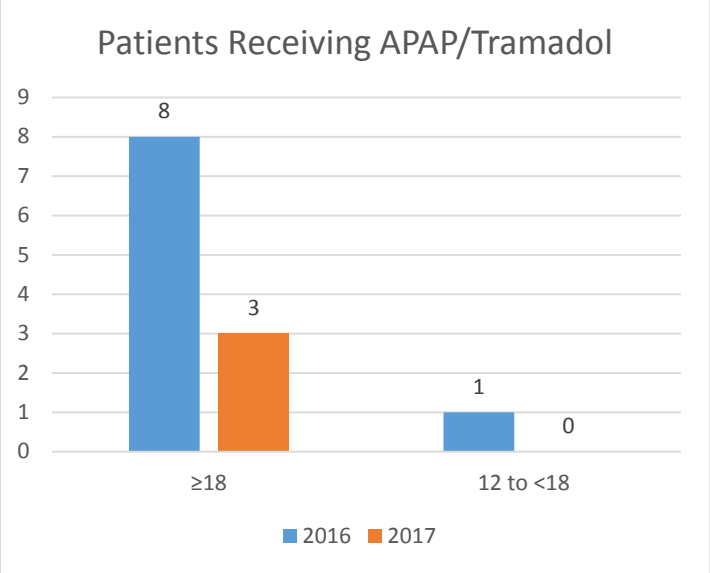

Pediatric Patients Receiving APAP/Codiene
40
35
30
25
20
15
10
5
0
15
8
36
2
12 to <18
<12
2016
2017

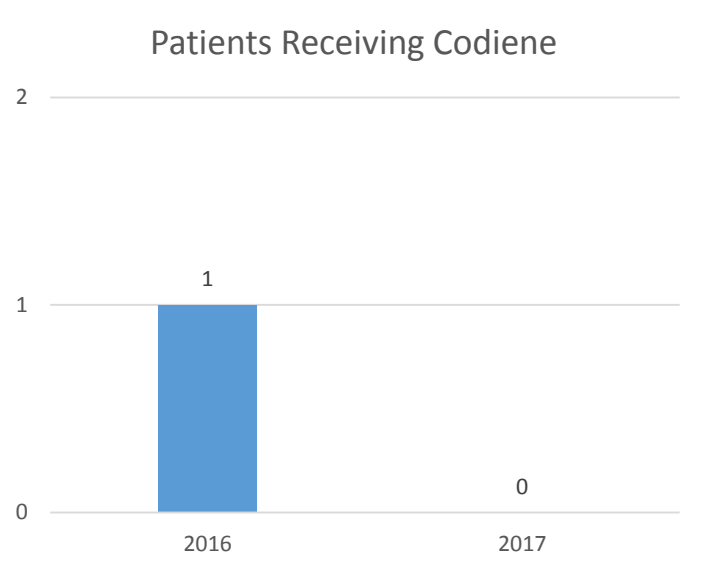

Adult Patients Receiving Promethazine/Codiene
80
75
70
65
60
55
78
65
2016
2017

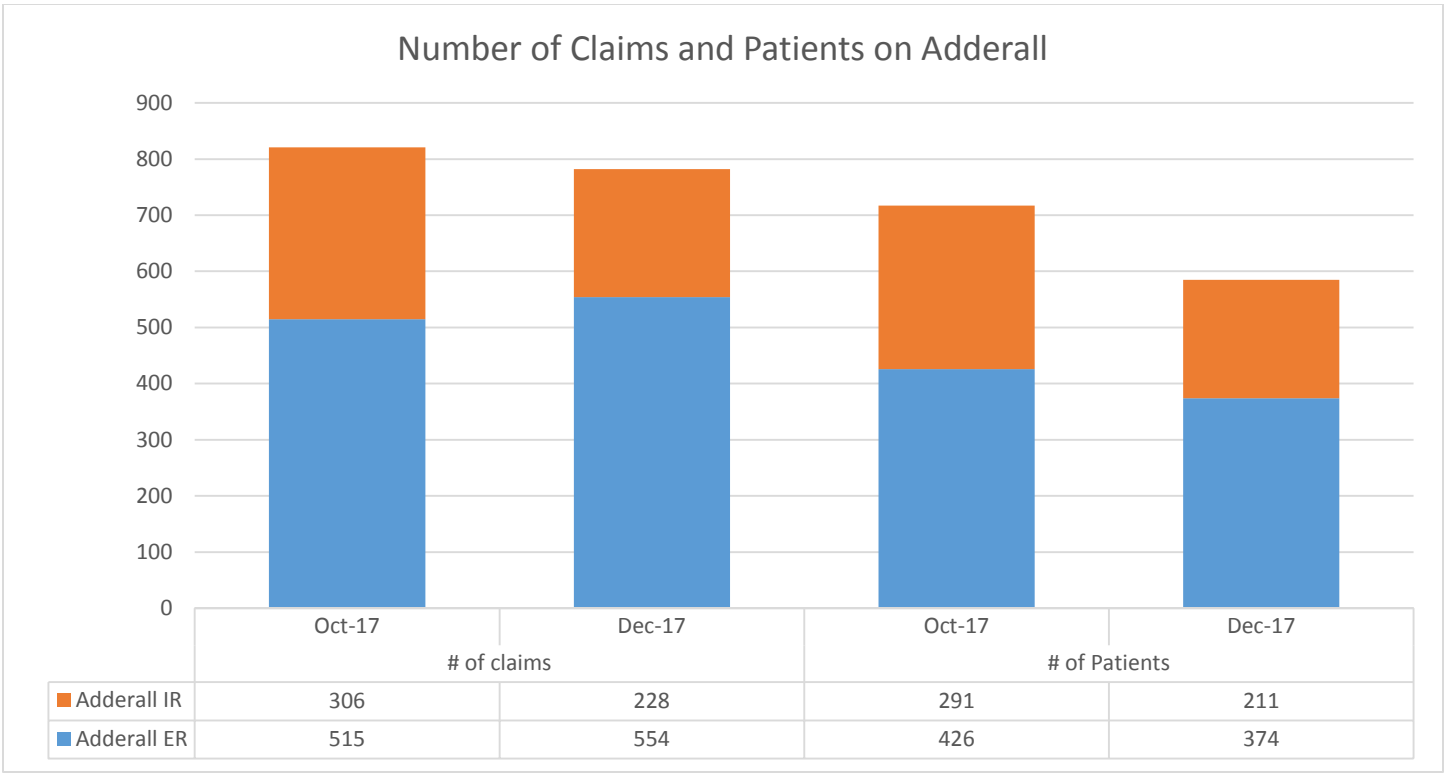

Pediatric Patients Receiving Promethazine/Codiene
16
14
12
10
8
6
4
2
0
12
6
15
0
12 to <18
<12
2016
2017


Adult Patients Receiving Codiene/Guaifenasin
57.5
57
56.5
56
55.5
55
54.5
54
53.5
53
52.5
57
54
2016
2017

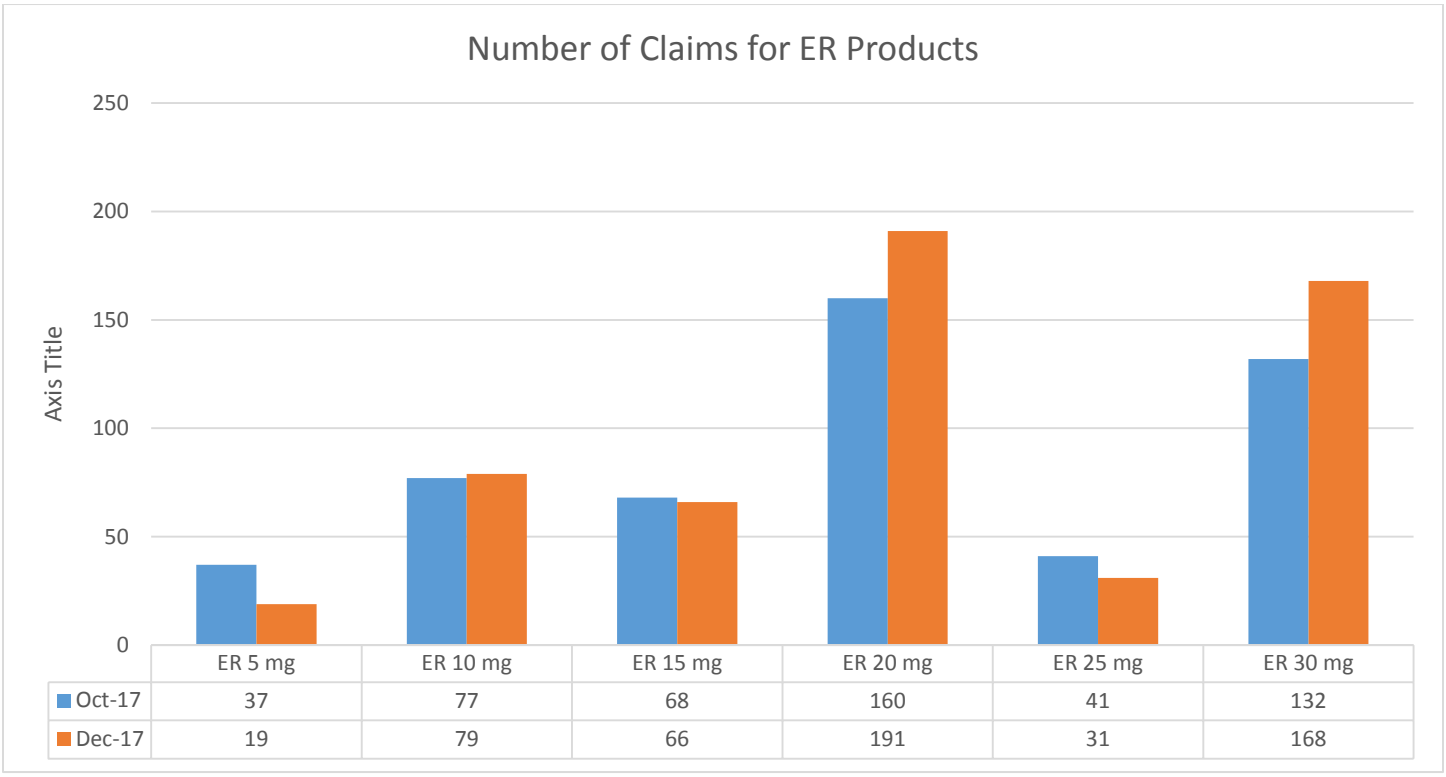

Pediatric Patients Recieving Codiene/Guaifenasin
18
16
14
12
10
8
6
4
2
0
9
9
16
2
12 to <18
<12
2016
2017


Patients Receiving APAP/Tramadol
9
8
7
6
5
4
3
2
1
0
8
3
1
0
≥18
12 to <18
2016
2017

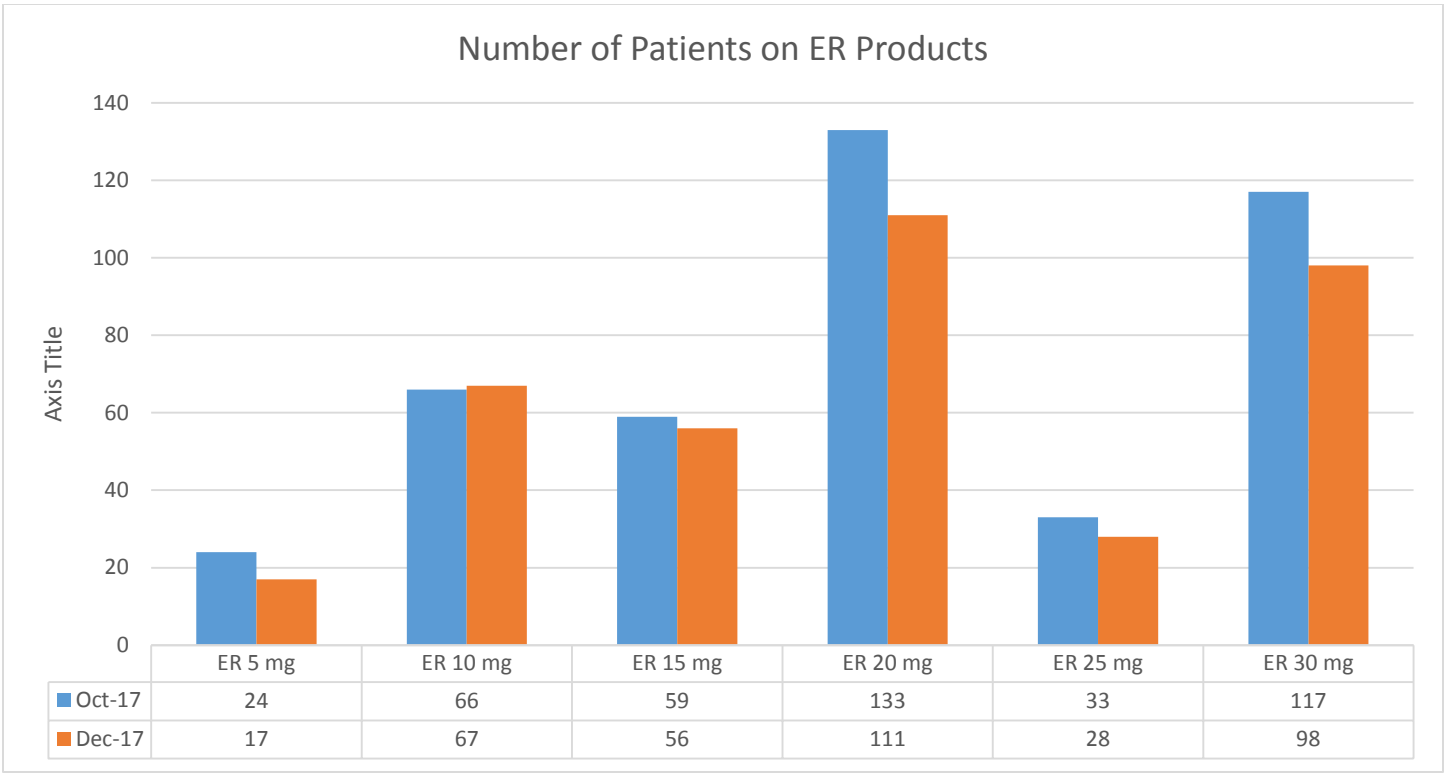

Patients Receiving Codiene
2
1
0
1
0
2016
2017



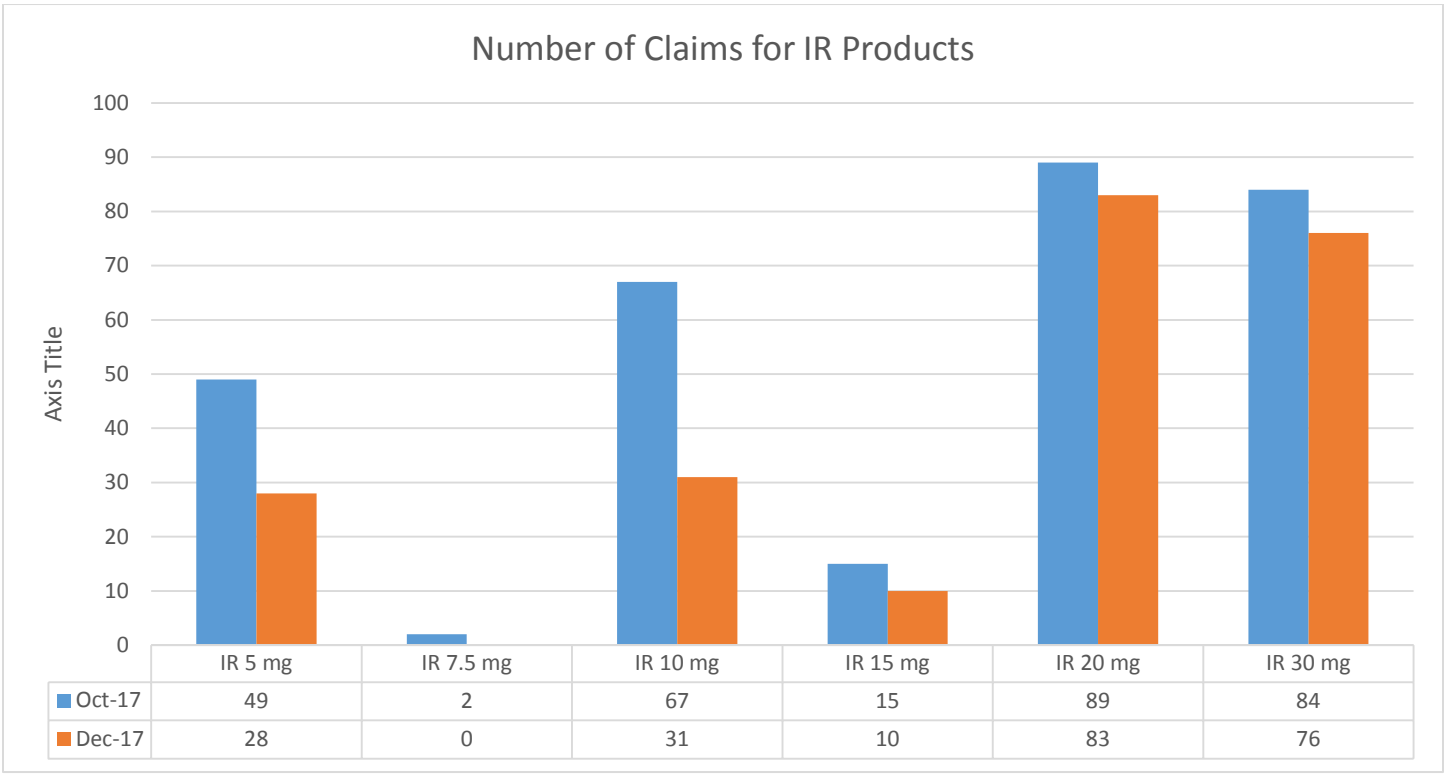
	# of claims		# of Patients	
	Oct-17	Dec-17	Oct-17	Dec-17
Adderall IR	306	228	291	211
Adderall ER	515	554	426	374



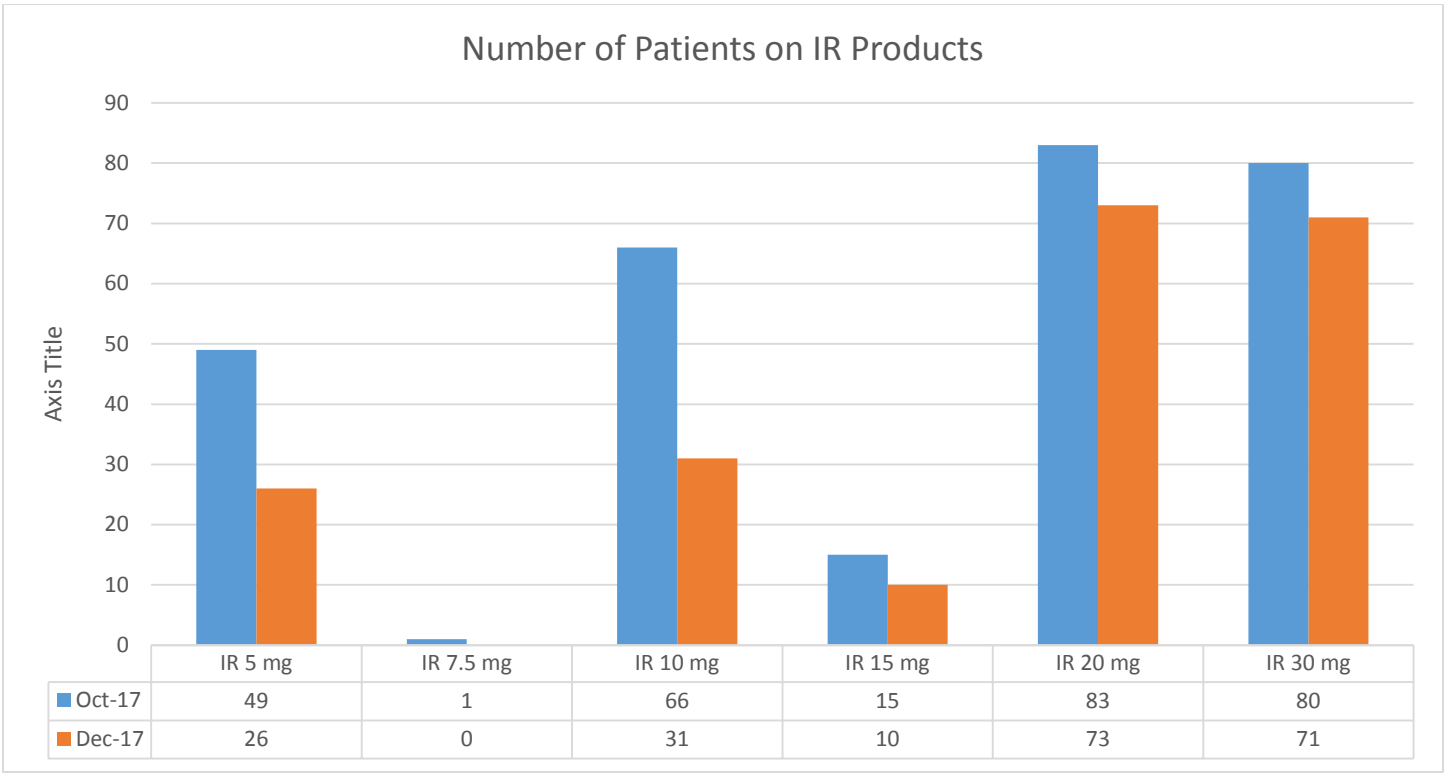
	ER 5 mg	ER 10 mg	ER 15 mg	ER 20 mg	ER 25 mg	ER 30 mg
Oct-17	37	77	68	160	41	132
Dec-17	19	79	66	191	31	168



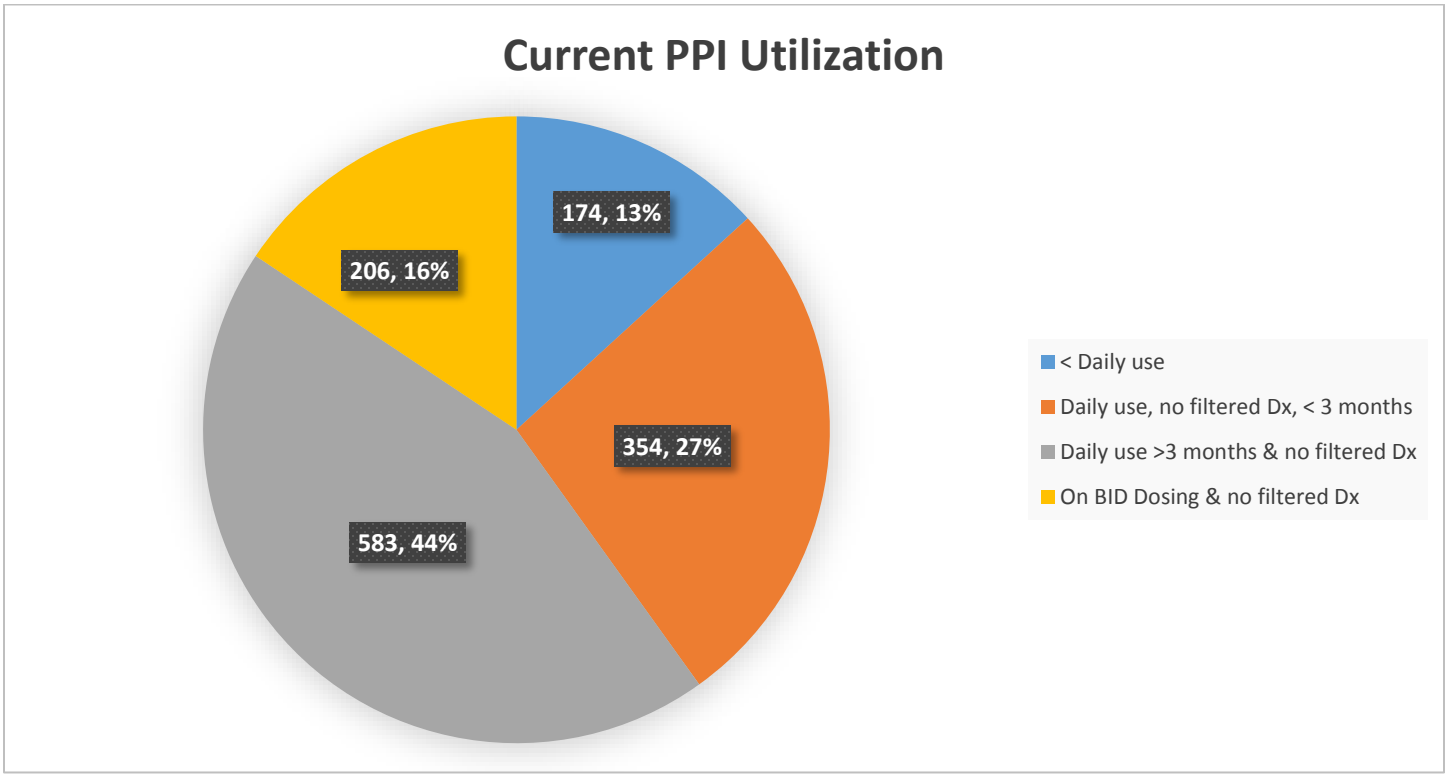
	ER 5 mg	ER 10 mg	ER 15 mg	ER 20 mg	ER 25 mg	ER 30 mg
Oct-17	24	66	59	133	33	117
Dec-17	17	67	56	111	28	98



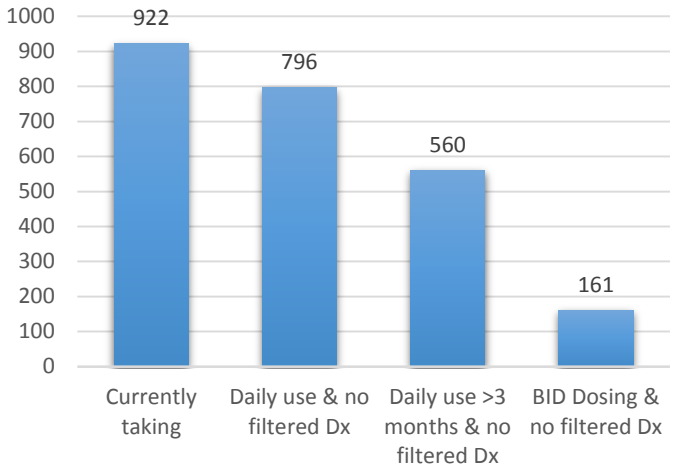
	IR 5 mg	IR 7.5 mg	IR 10 mg	IR 15 mg	IR 20 mg	IR 30 mg
Oct-17	49	2	67	15	89	84
Dec-17	28	0	31	10	83	76



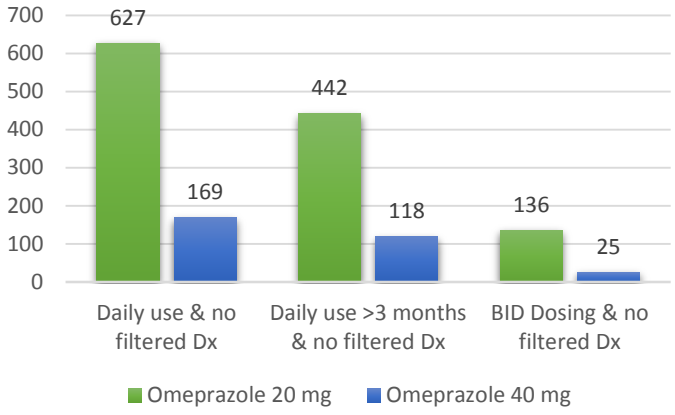
	IR 5 mg	IR 7.5 mg	IR 10 mg	IR 15 mg	IR 20 mg	IR 30 mg
Oct-17	49	1	66	15	83	80
Dec-17	26	0	31	10	73	71



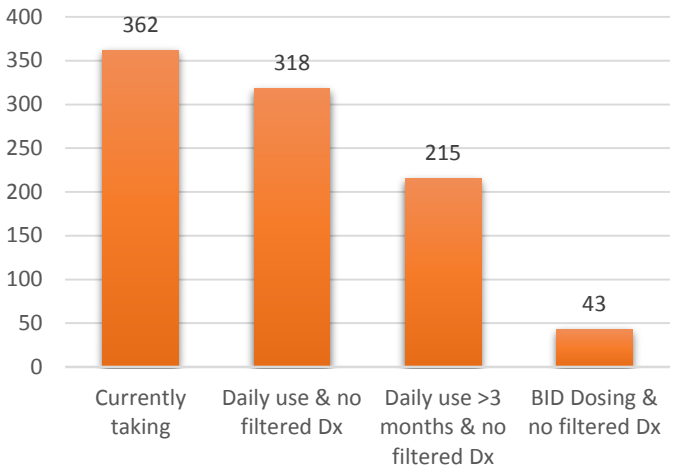
Patients Taking Omeprazole



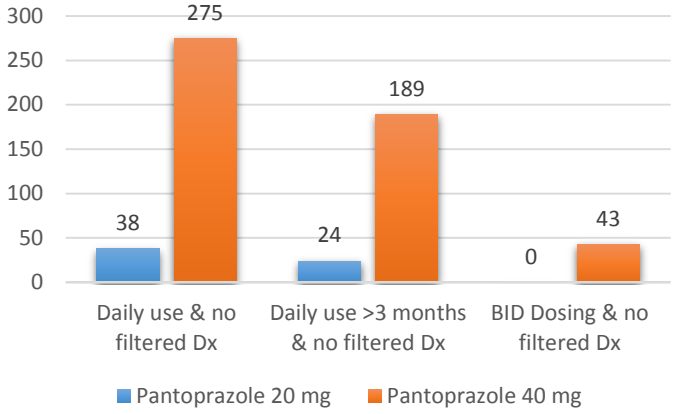
Patients Taking Omeprazole by Dose



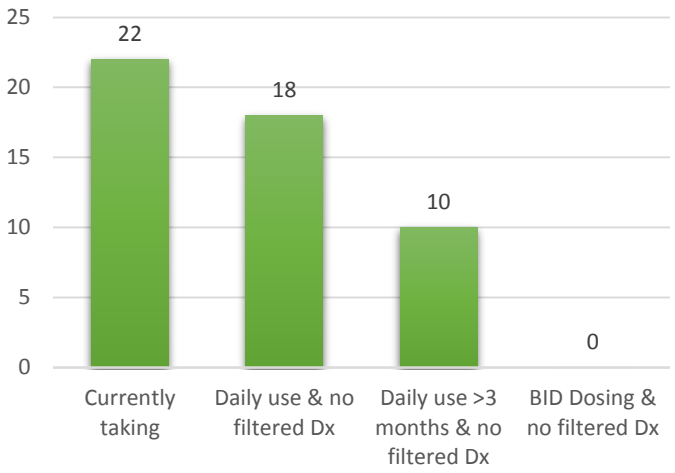
Patients Taking Pantoprazole



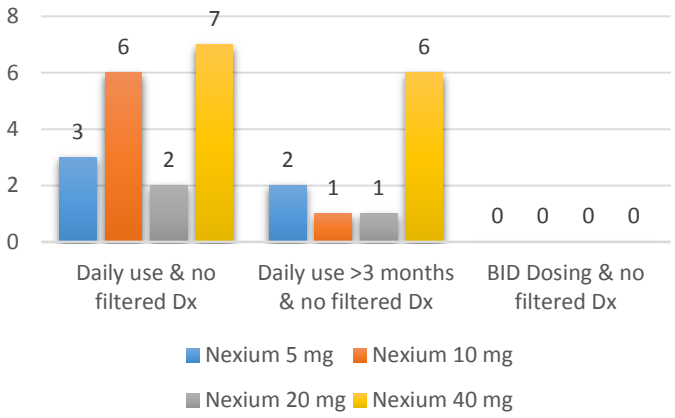
Patients Taking Pantoprazoloe by Dose

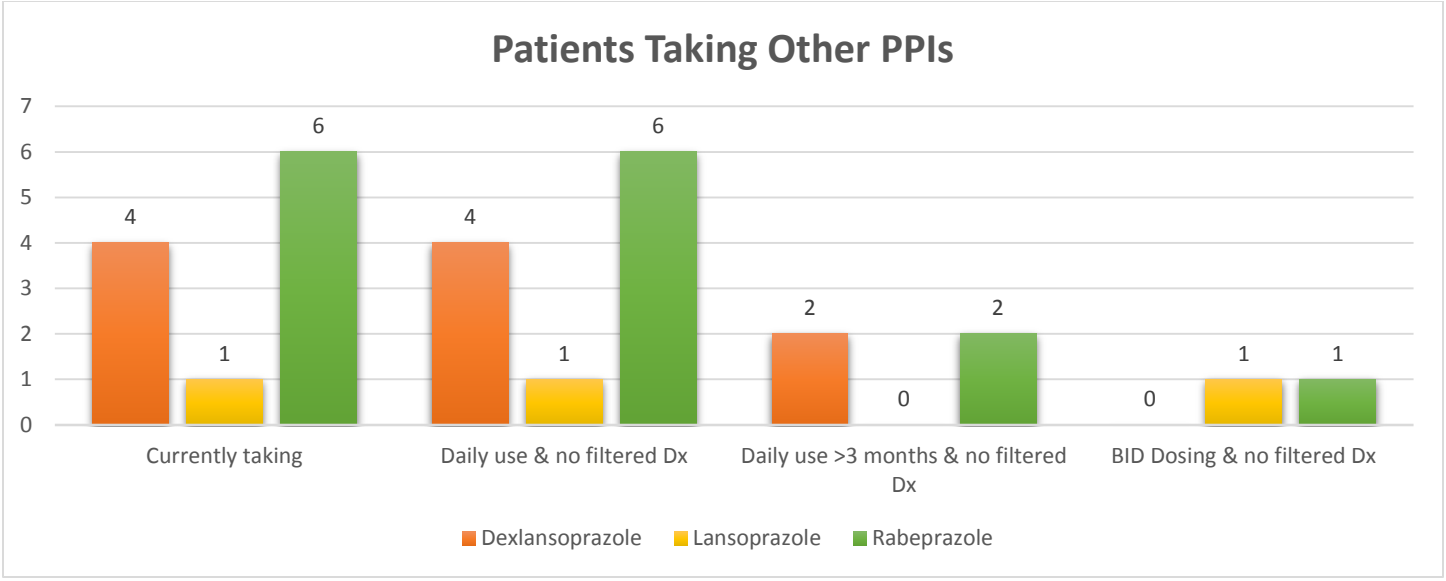


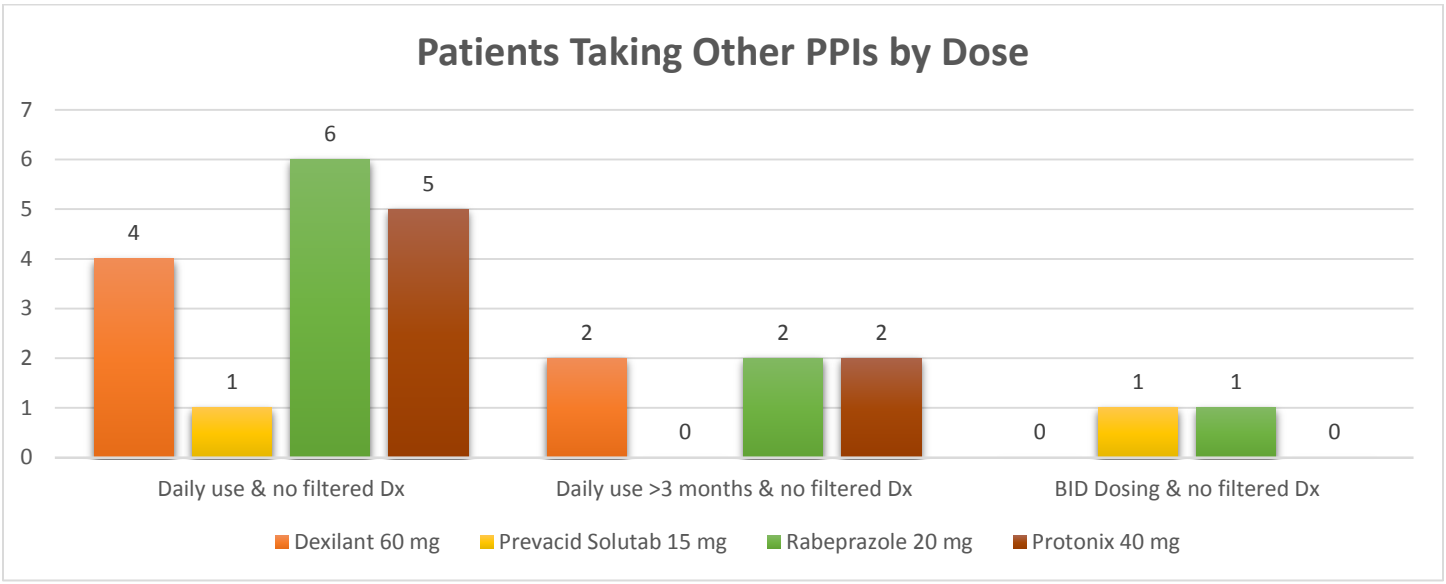
Patients Taking Esomeprazole



Patients Taking Esomeprazole by Dose




Patients Taking Other PPIs
7
6
5
4
3
2
1
0
4
1
6
4
1
6
2
0
2
0
1
1
Currently taking
Daily use & no filtered Dx
Daily use >3 months & no filtered Dx
BID Dosing & no filtered Dx
Dexlansoprazole
Lansoprazole
Rabeprazole


Patients Taking Other PPIs by Dose
7
6
5
4
3
2
1
0
4
1
6
5
2
0
2
2
0
1
1
0
Daily use & no filtered Dx
Daily use >3 months & no filtered Dx
BID Dosing & no filtered Dx
Dexilant 60 mg
Prevacid Solutab 15 mg
Rabeprazole 20 mg
Protonix 40 mg

NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
1ST QUARTER 2018

Criteria Recommendations ***Approved*** ***Rejected***

1. Fluticasone-Umeclidinium-Vilanterol / Overutilization _____ _____

Alert Message: The manufacturer's recommended dose of Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) is 1 inhalation (100 mcg fluticasone/62.5mcg umeclidinium/25mcg vilanterol) once daily by orally inhaled route only. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic-containing drugs.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Fluticasone/Umeclidinium/Vilanterol		

Max Dose: 100mcg fluticasone/62.5 mcg umeclidinium/25mcg vilanterol per day

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

2. Fluticasone-Umeclidinium-Vilanterol / Black Box Warning _____ _____

Alert Message: Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) contains the long-acting beta-2 adrenergic agonist (LABL) vilanterol and all LABAs increase the risk of asthma-related death. The safety and efficacy of fluticasone/umeclidinium/vilanterol) in patients with asthma have not been established. Fluticasone/umeclidinium/vilanterol is not indicated for the treatment of asthma.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Fluticasone/Umeclidinium/Vilanterol		Asthma

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

3. Fluticasone-Umeclidinium-Vilanterol/ Cardiovascular, Diabetes, Thyrotoxicosis & Convulsive Disorders _____ _____

Alert Message: Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) should be used with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis or sensitivity to sympathomimetic drugs. The vilanterol component is a sympathomimetic amine and can exacerbate these conditions.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Fluticasone/Umeclidinium/Vilanterol	Hypertension Arrhythmias Heart Failure Diabetes Seizures Epilepsy	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.

4. Fluticasone-Umeclidinium-Vilanterol / Strong CYP3A4 Inhibitors _____ _____

Alert Message: Concurrent use of Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) with a strong CYP3A4 inhibitor may result in increased systemic exposure to both fluticasone and vilanterol. Both vilanterol and fluticasone are CYP3A4 substrates and inhibition of their CYP3A4-mediated metabolism may increase exposure and risk of adverse effects.

Conflict Code: DD – Drug/Drug Interactions
Drugs/Diseases

Util A	Util B		Util C
Fluticasone/Umeclidinium/Vilanterol	Nefazodone	Saquinavir	
	Clarithromycin	Ritonavir	
	Cobicistat	Nelfinavir	
	Ketoconazole	Indinavir	
	Itraconazole	Boceprevir	
	Posaconazole		
	Voriconazole		

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

5. Fluticasone-Umeclidinium-Vilanterol / MAOIs, TCA & QT Prolong Meds _____ _____

Alert Message: Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) should be administered with extreme caution to patients being treated with MAOIs, TCAs, or drugs known to prolong the QTc interval or within 2 weeks of such agents. The action of the adrenergic agonist component of the combo product, vilanterol, on the cardiovascular system may be potentiated by these agents.

Conflict Code: DD – Drug/Drug Interactions
Drugs/Diseases

Util A	Util B				Util C
Trelegy	Albuterol	Disopyramide	Imipramine	Pazopanib	Thioridazine
	Alfuzosin	Dofetilide	Indapamide	Pentamidine	Tizanidine
	Amantadine	Dolasetron	Isradipine	Pimozide	Tolterodine
	Amiodarone	Doxepin	Itraconazole	Posaconazole	Trazodone
	Amitriptyline	Dronedarone	Ketoconazole	Procainamide	TMP/SMZ
	Amphetamine	Droperidol	Lapatinib	Propafenone	Trimipramine
	Arsenic Trioxide	Ephedrine	Levalbuterol	Protriptyline	Vandetanib
	Asenapine	Epinephrine	Levofloxacin	Quetiapine	Vardenafil
	Atazanavir	Erythromycin	Lithium	Quinidine	Venlafaxine
	Atomoxetine	Escitalopram	Metaproterenol	Ranolazine	Ziprasidone
	Azithromycin	Felbamate	Methadone	Risperidone	Zolmitriptan
	Chloral Hydrate	Flecainide	Moexipril/HCTZ	Ritonavir	Ezogabine
	Chloroquine	Fluconazole	Moxifloxacin	Salmeterol	Isocarboxazid
	Chlorpromazine	Fluoxetine	Nicardipine	Saquinavir	Phenelzine
	Ciprofloxacin	Foscarnet	Nilotinib	Sertraline	Tranylcypromine
	Citalopram	Fosphenytoin	Norfloxacin	Solifenacin	Linezolid
	Clarithromycin	Galantamine	Nortriptyline	Sotalol	
	Clomipramine	Gemifloxacin	Octreotide	Sunitinib	
	Clozapine	Granisetron	Ofloxacin	Tacrolimus	
	Dasatinib	Haloperidol	Ondansetron	Tamoxifen	
	Desipramine	Ibutilide	Paliperidone	Terbutaline	
	Diphenhydramine	Iloperidone	Paroxetine	Rasagiline	

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

6. Fluticasone-Umeclidinium-Vilanterol / Non-Potassium Sparing Diuretics _____ _____

Alert Message: Caution should be exercised when Trelegy Ellipta (fluticasone/umeclidinium/vilanterol), a beta-agonist containing combo agent, is prescribed concurrently with non-potassium sparing diuretics because concomitant administration may potentiate the ECG changes or hypokalemia that may result from administration of the diuretic.

Conflict Code: DD - Drug/Drug Interaction
Drugs/Diseases

Util A	Util B		Util C
Fluticasone/Umeclidinium/Vilanterol	Furosemide	Indapamide	
	Bumetanide	Methyclothiazide	
	Torsemide	Metolazone	
	Chlorothiazide		
	Chlorthalidone		
	HCTZ		

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

7. Fluticasone-Umeclidinium-Vilanterol / Nonselective Beta Blockers _____ _____

Alert Message: Concurrent use of a beta-adrenergic blocker with Trelegy Ellipta (fluticasone/umeclidinium/vilanterol), a beta2-agonist containing combo product, may diminish the pulmonary effect of the beta-agonist component, vilanterol. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with asthma and COPD. If concomitant therapy cannot be avoided, consider a cardioselective beta-blocker, but administer with caution.

Conflict Code: DD - Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Fluticasone/Umeclidinium/Vilanterol	Carvedilol	Acebutolol
	Nadolol	Atenolol
	Labetalol	Betaxolol
	Penbutolol	Bisoprolol
	Pindolol	Metoprolol
	Propranolol	Nebivolol
	Sotalol	
	Timolol	

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

8. Fluticasone-Umeclidinium-Vilanterol / Narrow Angle Glaucoma _____ _____

Alert Message: Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) should be used with caution in patients with narrow-angle glaucoma. The umeclidinium component of this combo product is an anticholinergic agent and its use in this patient population can worsen the condition.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Fluticasone/Umeclidinium/Vilanterol		Narrow Angle Glaucoma

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

9. Fluticasone-Umeclidinium-Vilanterol / Urinary Retention _____ _____

Alert Message: Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) should be used with caution in patients with urinary retention. The umeclidinium component of this combo product is an anticholinergic agent and its use can worsen urinary retention, especially in patients with prostatic hyperplasia or bladder neck obstruction.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Fluticasone/Umeclidinium/Vilanterol		Urinary Retention
		Bladder Neck Obstruction
		Prostatic Hyperplasia

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

10. Fluticasone-Umeclidinium-Vilanterol / Anticholinergics _____ _____

Alert Message: The concurrent use of Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) with anticholinergic agents should be avoided. The umeclidinium component of the combo product is an anticholinergic agent and concomitant use with other anticholinergics may lead to an increase in anticholinergic adverse effects.

Conflict Code: DD - Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Fluticasone/Umeclidinium/Vilanterol	Trihexyphenidyl	
	Benztropine	
	Orphenadrine	
	Darifenacin	
	Fesoterodine	
	Flavoxate	
	Oxybutynin	
	Solifenacin	
	Tolterodine	
	Trospium	
	Hyoscyamine	
	Scopolamine	
	Propantheline	
	Glycopyrrolate	
	Mepenzolate	
	Methscopolamine	
	Dicyclomine	

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

11. Fluticasone-Umeclidinium-Vilanterol / Hepatic Impairment _____ _____

Alert Message: Use of Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) in patients with hepatic impairment may result in increased systemic exposure to the fluticasone component in the combo agent. Fluticasone is primarily cleared in the liver and studies have shown fluticasone systemic exposure can increase by up to 3-fold in patients with hepatic impairment as compared to healthy subjects. Monitor patients for corticosteroid-related side effects.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Fluticasone/Umeclidinium/Vilanterol		Hepatic Impairment

References:
Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

12. Fluticasone-Umeclidinium-Vilanterol / Non-adherence _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Trelegy Ellipta (fluticasone/umeclidinium/vilanterol). Non-adherence to the prescribed dosing regimen may result in sub-therapeutic effects, which may lead to decreased outcomes and additional healthcare costs.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Fluticasone/Umeclidinium/Vilanterol		

References:

Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
van Boven JF, Chavannes NH, van der Molen T, et al. Clinical and Economic Impact of Non-Adherence in COPD: A Systematic Review. Respir Med. 2014 Jan;108(1):103-113.
Restrepo RD, Alvarez MT, Wittnebel LD, et al., Medication Adherence Issues in\Patients Treated for COPD. International Journal of COPD. 2008;3(3):371-384.
Simoni-Wastila L, Wei Y, Qian J, et al., Association of Chronic Obstructive\Pulmonary Disease Maintenance Medication Adherence With All-Cause\Hospitalization and Spending in a Medicare Population. Am Jrnl Geriatr\Pharmacother. 2012 Jun;10(3):201-210.
Lareau SC, Yawn BP. Improving Adherence with Inhaler Therapy in COPD.\International Journal of COPD. 2010 Nov 24;5:401-406.

13. Fluticasone-Umeclidinium-Vilanterol / Therapeutic Appropriateness _____ _____

Alert Message: Trelegy Ellipta (fluticasone/umeclidinium/vilanterol) is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Fluticasone/Umeclidinium/Vilanterol		

Age Range: < 18 yoa

References:

Trelegy Ellipta Prescribing Information, September 2017, GlaxoSmithKline.
Clinical Pharmacology, 2017 Elsevier/Gold Standard.

14. QVAR Redihaler / Nonadherence _____ _____

Alert Message: Non-adherence with prescribed asthma therapy may significantly increase the risk of asthma exacerbations, emergency room visits, hospitalization, and asthma-related deaths. Always verify at each office visit that the patient understands their condition, the treatment plan, and the importance of adherence.

Conflict Code: LR - Nonadherence
Drugs/Diseases

Util A	Util B	Util C
Beclomethasone breath actuated		

References:

Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
Williams LK, Pladevall M, XI Hy, et al., Relationship between Adherence to Inhaled Corticosteroids and Poor Outcomes Among Adults with Asthma. J Allerg Clin Immunol. December 2004;114(6):1288-1293.
Tan H, Sarawate C, Singer J et al., Impact of Asthma Controller Medications on Clinical, Economic, and Patient-Reported Outcomes. Mayo Clinic Proc. August 2009;84(8):675-684.

15. Armonair Respiclick / Nonadherence _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Armonair Respiclick (fluticasone). Nonadherence to the prescribed dosing regimen may result in sub-therapeutic effects, which may lead to decreased outcomes and additional healthcare costs.

Conflict Code: LR - Nonadherence
Drugs/Diseases
Util A Util B Util C
Fluticasone Inhalation Powder

References:
Iuga AO, McGuire MJ. Adherence and Health Care Costs. Risk Manag Healthc Policy. 2014 Feb 20;7:35-44.
Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
Tan H, Sarawate C, Singer J et al., Impact of Asthma Controller Medications on Clinical, Economic, and Patient-Reported Outcomes. Mayo Clinic Proc. August 2009;84(8):675-684.
LI JT, et al. Attaining Optimal Asthma Control: A Practice Parameter. J Allerg Clin Immunol. 2005;116"S3-11.
Bender BG, Overcoming Barriers to Nonadherence in Asthma Treatment. J Allerg Clin Immuno. June 2002;109(6):S554-559.

16. Armonair Respiclick / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Armonair Respiclick (fluticasone) in pediatric patients below the age of 12 years have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases
Util A Util B Util C
Fluticasone Inhalation Powder

Age Range: 0 – 11 yoa

References:
Armonair Prescribing Information, Jan. 2017, Teva Respiratory, LLC.
Clinical Pharmacology, 2017 Elsevier Gold Standard.

17. AirDuo Respiclick / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of AirDuo Respiclick (fluticasone/fluticasone) in pediatric patients below the age of 12 years have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases
Util A Util B Util C
Fluticasone/Salmeterol Inhalation Powder

References:
AirDuo Prescribing Information, Jan. 2017, Teva Respiratory, LLC.
Clinical Pharmacology, 2017 Elsevier Gold Standard.

18. AirDuo Respiclick / Nonadherence _____ _____

Alert Message: Non-adherence with prescribed asthma therapy may significantly increase the risk of asthma exacerbations, emergency room visits, hospitalization, and asthma-related deaths. Always verify at each office visit that the patient understands their condition, the treatment plan, and the importance of adherence.

Conflict Code: LR - Nonadherence
Drugs/Diseases

Util A	Util B	Util C
Fluticasone/Salmeterol Inhalation Powder		

References:
Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
Williams LK, Pladevall M, XI Hy, et al., Relationship between Adherence to Inhaled Corticosteroids and Poor Outcomes Among Adults with Asthma. J Allerg Clin Immunol. December 2004;114(6):1288-1293.
Tan H, Sarawate C, Singer J et al., Impact of Asthma Controller Medications on Clinical, Economic, and Patient-Reported Outcomes. Mayo Clinic Proc. August 2009;84(8):675-684.

19. Lesinurad/Allopurinol / Overutilization _____ _____

Alert Message: Duzallo (lesinurad/allopurinol) may be over-utilized. The manufacturer's recommended maximum dose is one 200 mg lesinurad/300mg allopurinol tablet once daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C (Negate)
Lesinurad/Allopurinol		CKD Stage 4 & 5 ESRD Dependence on Renal Dialysis Kidney Replace by Transplant

Max Dose: 200mg/300mg per day

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

20. Lesinurad/Allopurinol / Lesinurad _____ _____

Alert Message: Therapeutic duplication of lesinurad-containing products may be occurring.

Conflict Code: TD – Therapeutic Duplication
Drugs/Diseases

Util A	Util B	Util C
Lesinurad/Allopurinol	Lesinurad	

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

Criteria Recommendations *Approved* *Rejected*

21. Lesinurad/Allopurinol / Severe Renal Impairment _____ _____

Alert Message: The use of Duzallo (lesinurad/allopurinol) is contraindicated in patients with severe renal impairment (eCLcr < 30 mL/min), end-stage renal disease, kidney transplant recipients, or patients on dialysis. Lesinurad/allopurinol is not expected to be effective in these patient populations.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Lesinurad/Allopurinol		CKD Stage 4 & 5
		ESRD
		Dependence on Renal Dialysis
		Kidney Replace by Transplant

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

22. Lesinurad/Allopurinol / Mild to Moderate Renal Impairment _____ _____

Alert Message: Patients with moderate renal impairment receiving lesinurad have been shown to have a higher occurrence of renal related adverse reactions compared to patients with mild renal impairment or normal renal function. No dosage adjustment is recommended in patients with an eCLcr 45 to less than 60 mL/min, however frequent renal function monitoring is recommended. A lesinurad-containing agent should not be initiated in patients with an eCLcr less than 45 mL/min and should be discontinued when eCLcr is persistently less than 45 mL/min.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Lesinurad		CKD 2 & 3

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

23. Lesinurad/Allopurinol / Tumor Lysis Syndrome & Lesch-Nyhan Syndrome _____ _____

Alert Message: The use of Duzallo (lesinurad/allopurinol) is contraindicated in patients with tumor lysis syndrome or Lesch-Nyhan syndrome, where the rate of uric acid formation is greatly increased.

Conflict Code: MC – Drug (Actual) Disease Precaution/Warning
Drugs/Diseases

Util A	Util B	Util C
Lesinurad/Allopurinol	Tumor Lysis Syndrome	
	Lesch-Nyhan Syndrome	

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

24. Lesinurad/Allopurinol / Severe Hepatic Impairment _____ _____

Alert Message: The use of Duzallo (lesinurad/allopurinol) is not recommended in patients with severe hepatic impairment as it has not been studied in this patient population. No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B).

Conflict Code: MC – Drug (Actual) Disease Precaution/Warning

Util A	Util B	Util C
Lesinurad/Allopurinol	Cirrhosis	
	Hepatic Fibrosis	

References:

Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

25. Lesinurad/Allopurinol / Nonadherence _____ _____

Alert Message: Based on refill history, your patient may be underutilizing Duzallo (lesinurad/allopurinol). Nonadherence to the prescribed dosing regimen may result in sub-therapeutic effects, which may lead to decreased patient outcomes and additional healthcare costs.

Conflict Code: LR - Nonadherence
Drugs/Diseases

Util A	Util B	Util C
Allopurinol		

References:

Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med 2005; 353:487- 497.
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Harrold LR, Andrade SE, Briesacher BA, et al., Adherence with Urate-Lowering Therapies for the Treatment of Gout. Arthritis Res Ther. 2009;11(2).
De Vera MA, Marcotte G, Rai S, et al., Medication Adherence in Gout: A Systemic Review. Arthritis Care & Research. Vol. 66, No.10, October 2014, pp 1551-1559.

26. Lesinurad/Allopurinol / Moderate CYP2C9 Inhibitors _____ _____

Alert Message: Concurrent use of Duzallo (lesinurad/allopurinol) with moderate CYP2D9 inhibitors (e.g., fluconazole, amiodarone, and miconazole) should be done with caution. The lesinurad component of the combo product is a CYP2C9 substrate and concomitant use with a CYP2C9 inhibitor may result in increased lesinurad exposure and risk of lesinurad-related adverse effects

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Lesinurad/Allopurinol	Fluconazole	
	Amiodarone	
	Abiraterone	
	Sorafenib	
	Miconazole	

References:

Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

27. Lesinurad/Allopurinol / CYP2C9 Inducers _____ _____

Alert Message: Concurrent use of Duzallo (lesinurad/allopurinol) with CYP2C9 inducers (e.g., carbamazepine, rifampin, and enzalutamide) should be done with caution. The lesinurad component of the combo product is a CYP2C9 substrate and concomitant use with these agents may result in decreased lesinurad exposure and diminished therapeutic effect. Monitor patients for reduction in lesinurad/allopurinol efficacy or consider therapy modification.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Lesinurad/Allopurinol	Carbamazepine	
	Rifampin	
	Enzalutamide	

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

28. Lesinurad/Allopurinol / Epoxide Hydrolase Inhibitors _____ _____

Alert Message: Duzallo (lesinurad/allopurinol) should not be administered with an epoxide hydrolase inhibitor (i.e., valproic acid). Concurrent use of these agents may interfere with metabolism of lesinurad component of the combo product.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Lesinurad/Allopurinol	Valproic Acid	

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

29. Lesinurad/Allopurinol / Hormonal Contraceptives _____ _____

Alert Message: Hormonal contraceptives including oral, injectable, transdermal, and implantable forms may not be reliable when co-administered with Duzallo (lesinurad/allopurinol). Females should use additional methods of contraception and not rely on hormonal contraception alone when taking a lesinurad-containing product.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Lesinurad/Allopurinol	Oral Contraceptives	
	Injectable Contraceptives	
	Transdermal Contraceptives	
	Implantable Contraceptives	

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

30. Lesinurad/Allopurinol / Aspirin > 325 mg/day _____ _____

Alert Message: Aspirin, at doses higher than 325 mg per day may decrease the efficacy of Duzallo (lesinurad/allopurinol). Aspirin at doses of 325 mg or less per day (i.e., for cardiovascular protection) does not decrease the efficacy of lesinurad and can be co-administered with lesinurad.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Aspirin	Lesinurad/Allopurinol	

Max Dose: > 325 mg/day

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

31. Allopurinol / Thiazides _____ _____

Alert Message: Concurrent use of an allopurinol-containing agent and thiazide diuretics may contribute to the enhancement of allopurinol toxicity in some patients. Although a causal mechanism and a cause-and-effect relationship have not been established, current evidence suggests that renal function should be monitored in patients on thiazide diuretics and allopurinol even in the absence of renal failure, and dosage levels should be even more conservatively adjusted in those patients on such combined therapy if diminished renal function is detected.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Allopurinol	HCTZ	
Lesinurad/Allopurinol	Chlorothiazide	
	Methyclothiazide	
	Bendroflumethiazide	
	Chlorthalidone	
	Indapamide	
	Metolazone	

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

32. Lesinurad/Allopurinol / Therapeutic Appropriateness - Pediatrics _____ _____

Alert Message: The safety and effectiveness of Duzallo (lesinurad/allopurinol) have not been established in patients under 18 years of age.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Lesinurad		

Age Range: 0-17 yoa

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.

33. Sumatriptan/Naproxen / Overutilization _____ _____

Alert Message: Treximet (sumatriptan/naproxen) may be over-utilized. The manufacturer's recommended maximum daily dose in adults is two 85mg sumatriptan/500mg naproxen tablets taken at least 2 hours apart. The safety of treating an average of more than 5 migraine headaches in adults in in a 30-day period has not been established.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Sumatriptan/Naproxen		

Max Dose: 2 tablets per day
Age Range: 18-999 yoa

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Facts & Comparisons, 2017 Updates, Wolters Kluwer Health.

34. Sumatriptan/Naproxen / Overutilization 12 – 17 yoa _____ _____

Alert Message: Treximet (sumatriptan/naproxen) may be over-utilized. The manufacturer's recommended maximum daily dose in patients 12 to 17 years of age is one (85mg sumatriptan/500mg naproxen) tablet per day. The safety of treating an average of more than 2 migraine headaches in pediatric patients in a 30-day period has not been established.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Sumatriptan/Naproxen		

Max Dose: 1 tablet per day
Age Range: 12 – 17 yoa

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Facts & Comparisons, 2017 Updates, Wolters Kluwer Health.

35. Sumatriptan/Naproxen / Overutilization _____ _____

Alert Message: Treximet (sumatriptan/naproxen) use is contraindicated in patients with severe hepatic impairment.

Conflict Code: MC – Drug (Actual) Disease Precaution
Drugs/Diseases

Util A	Util B	Util C
Sumatriptan/Naproxen	Severe Hepatic Impairment	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Facts & Comparisons, 2017 Updates, Wolters Kluwer Health.

36. Sumatriptan/Naproxen / Overutilization _____ _____

Alert Message: Treximet (sumatriptan/naproxen) may be over-utilized. The manufacturer's recommended maximum daily dose in patients with mild to moderate hepatic impairment is one 10mg sumatriptan/60mg naproxen tablet per day.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Sumatriptan/Naproxen		Hepatic Impairment

Max Dose: 10mg sumatriptan/60mg naproxen

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Facts & Comparisons, 2017 Updates, Wolters Kluwer Health.

37. Sumatriptan/Naproxen / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Treximet (sumatriptan/naproxen) in pediatric patients under 12 years of age have not been established.

Conflict Code: TA - **T**herapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Sumatriptan/Naproxen		

Age Range: 0-11 yoa

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Facts & Comparisons, 2017 Updates, Wolters Kluwer Health.

38. Itraconazole Tabs / Dofetilide _____ _____

Alert Message: Concurrent use of Onmel (itraconazole tablets) with dofetilide is contraindicated. Concomitant use of these agents may result in serious and/or life-threatening events. Itraconazole is a potent CYP3A4 inhibitor and use with dofetilide, a CYP3A4 substrate, may result in elevated dofetilide plasma concentrations.

Conflict Code: DD – Drug/Drug Interactions
Drugs/Diseases

Util A	Util B	Util C
Itraconazole Tabs	Dofetilide	

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Onmel Prescribing Information, Nov. 2012, Merz Pharmaceuticals, LLC.

39. Itraconazole Tabs / Ticagrelor _____ _____

Alert Message: Concurrent use of Onmel (itraconazole tablets) with Brilinta (ticagrelor) is contraindicated. Concomitant use of these agents may result in serious and/or life-threatening events. Itraconazole is a potent CYP3A4 inhibitor and use with ticagrelor, a CYP3A4 substrate, may result in elevated ticagrelor plasma concentrations.

Conflict Code: DD – Drug/Drug Interactions
Drugs/Diseases

Util A	Util B	Util C
Itraconazole Tabs	Ticagrelor	

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Onmel Prescribing Information, Nov. 2012, Merz Pharmaceuticals, LLC.

40. Itraconazole Tabs / Triazolam _____ _____

Alert Message: Concurrent use of Onmel (itraconazole tablets) with triazolam is contraindicated. Concurrent use of these agents may result in serious and/or life-threatening events. Itraconazole if a potent CYP3A4 inhibitor and use with triazolam, a CYP3A4 substrate, may result in elevated triazolam plasma concentrations.

Conflict Code: DD – Drug/Drug Interactions
Drugs/Diseases

Util A	Util B	Util C
Itraconazole Tabs	Triazolam	

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Onmel Prescribing Information, Nov. 2012, Merz Pharmaceuticals, LLC.

41. Itraconazole Tabs / Midazolam (Oral) _____ _____

Alert Message: Concurrent use of Onmel (itraconazole tablets) with oral midazolam is contraindicated. Concomitant use of these agents may result in serious and/or life-threatening events. Itraconazole is a potent CYP3A4 inhibitor and use with oral midazolam, a CYP3A4 substrate, may result in elevated midazolam plasma concentrations.

Conflict Code: DD – Drug/Drug Interactions
Drugs/Diseases

Util A	Util B	Util C
Itraconazole Tabs	Midazolam - oral	

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Onmel Prescribing Information, Nov. 2012, Merz Pharmaceuticals, LLC.

42. Dupilumab / Overutilization _____ _____

Alert Message: The recommended dose of Dupixent (dupilumab) for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Dupilumab		

Maintenance Max Dose: 300mg every other week.

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Dupixent Prescribing Information, March 2017, Regeneron Pharmaceuticals, Inc.

43. Dupilumab / Asthma _____ _____

Alert Message: Dupixent (dupilumab) is an interleukin-4 receptor alpha antagonist which may improve asthma symptoms. Advise patients with co-morbid asthma receiving dupilumab not to adjust or stop their asthma treatments without consultation with their physicians. Safety and efficacy of dupilumab have not been established in the treatment of asthma.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C (Include)
Dupilumab		Asthma

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Dupixent Prescribing Information, March 2017, Regeneron Pharmaceuticals, Inc.

44. Dupilumab / Therapeutic Appropriateness - Age _____ _____

Alert Message: Safety and efficacy of Dupixent (dupilumab) in pediatric patients (<18 years of age) have not been established.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Dupilumab		

Age Range: < 18 yoa

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Dupixent Prescribing Information, March 2017, Regeneron Pharmaceuticals, Inc.

45. QVAR Redihaler / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Qvar Redihaler (beclomethasone) in pediatric patients below the age of 4 years have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Beclomethasone breath actuated		

Age Range: < 4 yoa

References:
QVAR Redihaler Prescribing Information, August 2017, Teva Pharmaceuticals, LLC,
Clinical Pharmacology, 2017 Elsevier Gold Standard.

46. Naldemedine / Overutilization _____ _____

Alert Message: Symproic (naldemedine) may be over-utilized. The manufacturer's recommended dosage of naldemedine, for the treatment of opioid-induced constipation in patients with chronic non-cancer pain, is 0.2 mg once daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Naldemedine		

Max Dose: 0.2 mg/day

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

47. Naldemedine / Opiate Agonists _____ _____

Alert Message: The review of the patient's drug history did not reveal current use of opioid medication. Symproic (naldemedine) is approved for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain. Naldemedine should be discontinued if treatment with the opioid medication is discontinued.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Naldemedine		Meperidine
		Morphine
		Codeine
		Hydrocodone
		Oxycodone
		Oxymorphone
		Levorphanol
		Fentanyl
		Tramadol
		Tapentadol

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

48. Naldemedine / Gastrointestinal Obstruction _____ _____

Alert Message: Symproic (naldemedine) use is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation. Monitor patients for development of severe, persistent, or worsening abdominal pain and discontinue in patients who develop this symptom.

Conflict Code: TA – Therapeutic Appropriateness (Contraindication)
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Naldemedine		Gastrointestinal Obstruction

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

49. Naldemedine / Reduction in GI Wall Integrity _____ _____

Alert Message: Symproic (naldemedine), a peripherally acting opioid antagonist, should be used with caution in patients with conditions that may result in impaired integrity of the gastrointestinal tract wall. Cases of gastrointestinal perforation have been reported in patients receiving another peripherally acting opioid antagonist who had conditions associated with localized reduction of structural integrity in the wall of the gastrointestinal tract. Monitor patients for the development of severe, persistent, or worsening abdominal pain and discontinue naldemedine in patients who develop these symptoms.

Conflict Code: TA – Therapeutic Appropriateness (Warning)
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Naldemedine		Crohn's Disease
		Peptic, Gastric, Duodenal & Gastrojejunal Ulcer Disease
		Perforation of Intestine
		Diverticular Disease of Intestine
		Malignant Neoplasm of Intestine
		Malignant Neoplasm of Stomach

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

50. Naldemedine / Therapeutic Appropriateness _____ _____

Alert Message: Safety and effectiveness of Symproic (naldemedine) have not been established in pediatric patients.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Naldemedine		

Age Range: 0 – 17 yoa

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

51. Naldemedine / Severe Hepatic Impairment _____ _____

Alert Message: Symproic (naldemedine) has not been studied in patients with severe hepatic impairment and use should be avoided in these patients. No dose adjustment of naldemedine is required in patients with mild or moderate hepatic impairment.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Naldemedine		Severe Hepatic Impairment

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

52. Naldemedine / Strong CYP3A4 Inducers _____ _____

Alert Message: Concomitant use of Symproic (naldemedine) with strong CYP3A4 inducers (e.g., phenytoin, rifampin, and carbamazepine) should be avoided. Naldemedine is a CYP3A4 substrate and concomitant use with a strong CYP3A4 inducer may result in decreased exposure of naldemedine leading to reduced efficacy.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Naldemedine	Phenobarbital	
	Primidone	
	Phenytoin	
	Carbamazepine	
	Rifampin	
	Rifabutin	
	Rifapentine	

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

53. Naldemedine / Other Opioid Antagonists _____ _____

Alert Message: The concurrent use of opioid antagonists should be avoided. Concomitant use of these agents may have an additional effect of opioid receptor antagonism and increased risk of opioid withdrawal.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Naldemedine	Methylnaltrexone	
	Naloxegol	

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

54. Naldemedine / Moderate & Strong CYP3A4 inhibitors _____ _____

Alert Message: The concurrent use of Symproic (naldemedine), a CYP3A4 substrate, with a moderate or strong CYP3A4 inhibitor may result in increased naldemedine plasma concentrations. Monitor patients in concurrent therapy for naldemedine-related adverse reactions (e.g., gastroenteritis, diarrhea, abdominal pain).

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B			Util C
Naldemedine	Nefazodone	Fluconazole	Nelfinavir	
	Clarithromycin	Aprepitant	Cobicistat	
	Telithromycin	Diltiazem	Atazanavir	
	Itraconazole	Verapamil	Fluvoxamine	
	Ketoconazole	Fosamprenavir	Crizotinib	
	Voriconazole	Idelalisib		
	Posaconazole	Cimetidine		
	Saquinavir	Ciprofloxacin		
	Ritonavir	Erythromycin		
	Indinavir	Dronedarone		

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors\and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Drug\InteractionaLabeling/ucm093664.htm

55. Naldemedine / P-Glycoprotein Inhibitors _____ _____

Alert Message: The concurrent use of Symproic (naldemedine), a P-gp substrate, with a P-gp inhibitor (e.g., amiodarone, verapamil, and ranolazine) may result in increased naldemedine plasma concentrations. Monitor patients on concurrent therapy for naldemedine-related adverse reactions (e.g., gastroenteritis, diarrhea, abdominal pain).

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B		Util C
Naldemedine	Amiodarone	Propafenone	
	Captopril	Quinidine	
	Carvedilol	Ranolazine	
	Clarithromycin	Ritonavir	
	Cyclosporine	Verapamil	
	Dronedarone	Itraconazole	
	Lapatinib	Ketoconazole	

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.
FDA: Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Drug\InteractionaLabeling/ucm093664.htm

56. Naldemedine / Pregnancy / Pregnancy Negating _____ _____

Alert Message: There is no available data with Symproic (naldemedine) in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. There is a potential for opioid withdrawal in a fetus when naldemedine is used in pregnant women. Naldemedine should be used during pregnancy only if the potential benefit justifies the potential risk.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negate)**
Naldemedine	Pregnancy	Delivery
		Miscarriage
		Abortion

Gender: Female
Age Range 11 – 50 yoa

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

57. Naldemedine / Lactation & Disorders of Lactation _____ _____

Alert Message: There is no information regarding the presence of Symproic (naldemedine) in human milk. Naldemedine has been shown to be present in the milk of rats. Because of the potential for serious adverse reactions, including opioid withdrawal in breastfed infants, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued in order to minimize drug exposure to a breasted infant, advise women that breastfeeding may be resumed 3 days after the final dose of naldemedine.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Naldemedine	Lactation	
	Other Disorder of Lactation	

Gender: Female
Age Range 11 – 50 yoa

References:
Facts & Comparisons, 2017 Wolters Kluwer Health.
Symproic Prescribing Information, March 2017, Shionogi Inc.

58. Glecaprevir/Pibrentasvir / Overutilization _____ _____

Alert Message: The manufacturer's recommended maximum daily dose of Mavyret (glecaprevir/pibrentasvir) is three tablets taken once daily with food (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg).

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir		

Max Dose: 3 tablets/day

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.

59. Glecaprevir/Pibrentasvir / Hepatic Impairment _____ _____

Alert Message: Mavyret (glecaprevir/pibrentasvir) is not recommended in patients with moderate hepatic impairment (Child-Pugh B) as safety and efficacy has not been established. Glecaprevir/pibrentasvir is contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to higher exposure of glecaprevir and pibrentasvir. No dosage adjustment is required in patients with mild hepatic impairment.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Glecaprevir/Pibrentasvir		Hepatic Impairment

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.

60. Glecaprevir/Pibrentasvir / Atazanavir _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with atazanavir-containing agents is contraindicated due to the increased risk of ALT elevations. In a drug interaction study co-administration of atazanavir/rtv with glecaprevir/pibrentasvir resulted in a significant increase in both glecaprevir and pibrentasvir exposure.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Atazanavir	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.

61. Glecaprevir/Pibrentasvir / Rifampin _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with rifampin is contraindicated due to the potential for loss of antiviral efficacy. Both components of the antiviral agent are P-gp substrates and co-administration with rifampin, a P-gp inducer, has been shown to significantly decrease glecaprevir and pibrentasvir exposure.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Rifampin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.

62. Glecaprevir/Pibrentasvir / Carbamazepine _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with carbamazepine is not recommended due to the potential for loss of antiviral efficacy. Both components of the antiviral agent are P-gp substrates and co-administration with carbamazepine, a P-gp inducer, has been shown to decrease glecaprevir and pibrentasvir exposure.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Carbamazepine	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.

63. Glecaprevir/Pibrentasvir / Efavirenz _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with an efavirenz-containing agent is not recommended due to the potential for loss of antiviral efficacy. Both components of the antiviral agent are P-gp substrates and co-administration with efavirenz, a P-gg inducer, has been shown to decrease glecaprevir and pibrentasvir exposure.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Efavirenz	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.

64. Glecaprevir/Pibrentasvir / Lopinavir/rtv _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with Kaletra (lopinavir/rtv) is not recommended due to the risk of increased glecaprevir and pibrentasvir exposure. Both components of the antiviral agent are substrates for P-gp and BCRP transporters and glecaprevir is also an OATP1B1/3 substrate. Lopinavir/rtv can inhibit OATP, P-gp, and BCRP transporters and co-administration with the antiviral agent may result in elevated antiviral plasma concentrations.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Lopinavir/rtv	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.
Mavyret (glecaprevir/pibrentasvir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209395Orig1s000. August 3, 2017.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000ClinPharmR.pdf

65. Glecaprevir/Pibrentasvir / Darunavir / Ritonavir _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with ritonavir-boosted Prezista (darunavir) is not recommended due to the risk of increased glecaprevir and pibrentasvir exposure. Both components of the antiviral agent are substrates for P-gp and BCRP transporters and glecaprevir is also an OATP1B1/3 substrate. Co-administration with the antiviral agent with the protease inhibitor regimen may result in elevated antiviral plasma concentrations.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Glecaprevir/Pibrentasvir	Darunavir	Ritonavir

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.
Mavyret (glecaprevir/pibrentasvir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209395Orig1s000. August 3, 2017.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000ClinPharmR.pdf

66. Glecaprevir/Pibrentasvir / Digoxin _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with digoxin may result in increased digoxin plasma concentrations. Digoxin serum concentrations should be measured before initiating glecaprevir/pibrentasvir and monitored during therapy. If digoxin concentrations need to be reduced the manufacturer recommends decreasing the digoxin dose by approximately 50% or by modifying the dosing frequency and continue monitoring.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Digoxin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.

67. Glecaprevir/Pibrentasvir / Ethinyl Estradiol-Containing Products _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with an ethinyl estradiol-containing product is not recommended due to the increased risk of ALT elevations. The mechanism of this interaction is unknown.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Ethinyl Estradiol-Containing Products	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.

68. Glecaprevir/Pibrentasvir / Atorvastatin - All _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with an atorvastatin-containing agent is not recommended. Co-administration of these agents may result in elevated atorvastatin plasma concentrations and risk of myopathy, including rhabdomyolysis. Atorvastatin is a substrate of CYP3A4 isozyme and P-gp and OATP1B1 transporters and both glecaprevir and pibrentasvir are P-gp and OATP1B1 transport inhibitors as well as weak inhibitors of CYP3A-mediated metabolism.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Atorvastatin	
	Atorvastatin/Amlodipine	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.
Mavyret (glecaprevir/pibrentasvir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209395Orig1s000. August 3, 2017.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000ClinPharmR.pdf

69. Glecaprevir/Pibrentasvir / Lovastatin _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with lovastatin is not recommended. Co-administration of these agents may result in elevated lovastatin plasma concentrations and risk of myopathy, including rhabdomyolysis. Lovastatin is a substrate of CYP3A4 isozyme, and P-gp and OATP1B1 transporters and both glecaprevir and pibrentasvir are P-gp and OATP1B1 transport inhibitors as well as weak inhibitors of CYP3A-mediated metabolism.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Lovastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.
Mavyret (glecaprevir/pibrentasvir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209395Orig1s000. August 3, 2017.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000ClinPharmR.pdf

70. Glecaprevir/Pibrentasvir / Simvastatin - All _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with a simvastatin-containing agent is not recommended. Co-administration of these agents may result in elevated simvastatin plasma concentrations and risk of myopathy, including rhabdomyolysis. Simvastatin is a substrate for CYP3A4 isozyme and P-gp and OATP1B1 transporters and both glecaprevir and pibrentasvir are P-gp and OATP1B1 transport inhibitors as well as weak inhibitors of CYP3A4-mediated metabolism.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Simvastatin	
	Simvastatin/Ezetimibe	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.
Mavyret (glecaprevir/pibrentasvir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209395Orig1s000. August 3, 2017.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000ClinPharmR.pdf

71. Glecaprevir/Pibrentasvir / Pravastatin _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with pravastatin may result in increased pravastatin plasma concentrations and risk of myopathy, including rhabdomyolysis. The manufacturer recommends that the pravastatin dose be reduce by 50% when co-administered with glecaprevir/pibrentasvir. Pravastatin is a substrate for P-gp, OATP1B1/3, and BCRP transporters and both glecaprevir and pibrentasvir are inhibitors of P-gp, OATP1B1/3, and BCRP transport.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Pravastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.
Mavyret (glecaprevir/pibrentasvir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209395Orig1s000. August 3, 2017.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000ClinPharmR.pdf

72. Glecaprevir/Pibrentasvir / Rosuvastatin _____ _____

Alert Message: The dose of rosuvastatin should not exceed 10 mg per day when co-administered with Mavyret (glecaprevir/pibrentasvir). The concurrent use of rosuvastatin with glecaprevir/pibrentasvir has been shown to increase rosuvastatin plasma concentrations which may increase the risk of rosuvastatin-related myopathy, including rhabdomyolysis. Rosuvastatin is a substrate for OATP1B1/3 and BCRP transporters and both glecaprevir and pibrentasvir are OATP1B1 and BCRP transport inhibitors.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Rosuvastatin 20 & 40mg	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.
Mavyret (glecaprevir/pibrentasvir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209395Orig1s000. August 3, 2017.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000ClinPharmR.pdf

73. Glecaprevir/Pibrentasvir / Fluvastatin _____ _____

Alert Message: The concurrent use of Mavyret (glecaprevir/pibrentasvir) with fluvastatin may result in increased fluvastatin plasma concentrations and risk of myopathy, including rhabdomyolysis. The manufacturer recommends using the lowest approved fluvastatin dose and if higher doses are needed, use the lowest necessary dose based on risk/benefit assessment. Fluvastatin is a substrate for OATP1B1/3 and BCRP transporters and the glecaprevir and pibrentasvir are inhibitors of both OATP1B1/3 and BCRP transporters.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Fluvastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.
Mavyret (glecaprevir/pibrentasvir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209395Orig1s000. August 3, 2017.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000ClinPharmR.pdf
Kellick KA, Bottorff M, Toth PP. A Clinician's Guide to Statin Drug-Drug Interactions. Jrnl of Clin Lipidol. 2014;8, S30-S46.

74. Glecaprevir/Pibrentasvir / Pitavastatin _____ _____

Alert Message: Concurrent use of Mavyret (glecaprevir/pibrentasvir) with pitavastatin may result in increased pitavastatin plasma concentrations and risk of myopathy, including rhabdomyolysis. The manufacturer recommends using the lowest approved pitavastatin dose and if higher doses are needed, use the lowest necessary dose based in risk/benefit assessment. Pitavastatin is a substrate for OATP1B1/3, and BCRP transporters and both glecaprevir and pibrentasvir are inhibitors of OATP1B1/3 and BCRP transport.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir	Pitavastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.
Mavyret (glecaprevir/pibrentasvir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209395Orig1s000. August 3, 2017.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000ClinPharmR.pdf
Kellick KA, Bottorff M, Toth PP. A Clinician's Guide to Statin Drug-Drug Interactions. Jrnl of Clin Lipidol. 2014;8, S30-S46.

75. Glecaprevir/Pibrentasvir / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Mavyret (glecaprevir/pibrentasvir) have not been established in children less than 18 years of age.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Glecaprevir/Pibrentasvir		

Age Range: 0-17 yoa

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Mavyret Prescribing Information, August 2017, AbbVie Inc.

76. Vosevi / Overutilization _____ _____

Alert Message: The manufacturer's recommended maximum dose of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is one table per day.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir		

Max Dose: 1 tablet per day

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

77. Vosevi / Hepatic Impairment _____ _____

Alert Message: Vosevi (sofosbuvir/velpatasvir/voxilaprevir) use is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C) due to higher exposure of the voxilaprevir component (up to 6-fold in non-HCV infected subjects).

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Sofosbuvir/Velpatasvir/Voxilaprevir		Hepatic Impairment

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

78. Vosevi / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) have not been established in pediatric patients.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir		

Age Range: 0-17 yoa

References:
Clinical Pharmacology, 2016 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

79. Vosevi / Rifampin _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with rifampin is contraindicated. Concomitant use of these agents may result in a significant decrease in the plasma concentrations of each of the components of the antiviral combination product leading to reduced therapeutic effect. Rifampin is a P-gp inducer as well as a potent CYP3A4 inducer. Each component of the antiviral is a P-gp substrate and velpatasvir and voxilaprevir are CYP3A4 substrates.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Rifampin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

80. Vosevi / Amiodarone _____ _____

Alert Message: Concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with amiodarone is not recommended. Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta-blockers, or those with underlying cardiac comorbidities, and/or advanced liver disease. In patients without alternative viable treatment options, cardiac monitoring is recommended.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Amiodarone	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

81. Vosevi / P-gp Inducers, Mod to Potent CYP2B6, 2C8 & 3A4 Inducers _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with inducers of P-gp and/or moderate or potent inducers of CYP2B6, CYP2C8, or CYP3A4 is not recommended. Co-administration of these agents may significantly decrease plasma concentrations of sofosbuvir, velpatasvir and/or voxilaprevir leading to potentially reduced antiviral therapeutic effects.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B		Util C
Sofosbuvir/Velpatasvir	Carbamazepine	Enzalutamide	
	Phenobarbital	Bosentan	
	Primidone	Efavirenz	
	Phenytoin	Etravirine	
	Oxcarbazepine	Nevirapine	
	Rifapentine	Modafinil	
	Rifabutin		

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.
Drug Development and Drug Interactions: Tables of Substrates, Inhibitors and Inducers. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Drug\InteractionaLabeling/ucm093664.htm

82. Vosevi / Antacids _____ _____

Alert Message: It is recommended to separate the administration of an antacid and Vosevi (sofosbuvir/velpatasvir/voxilaprevir) by 4 hours. The velpatasvir component of the antiviral combo product is pH dependent and use with drugs that increase gastric pH are expected to decreased velpatasvir, and therefore its bioavailability.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Aluminum hydroxide	
	Magnesium hydroxide	
	Calcium Carbonate	
	Sodium Bicarbonate	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

83. Vosevi / H2 Blockers _____ _____

Alert Message: Caution should be exercised when using Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with an H-2 receptor antagonist. These agents may be administered simultaneously or separated by 12 hours. The H-2 antagonist dose should not exceed a dose that is comparable to famotidine 40 mg twice daily. The velpatasvir component of the antiviral combo product is pH dependent and drugs that increase gastric pH are expected to decrease velpatasvir solubility, and therefore it bioavailability.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Cimetidine > 1600mg/day		Sofosbuvir/Velpatasvir/Voxilaprevir
Famotidine > 80mg/day		
Ranitidine > 600mg/day		
Nizatidine > 600mg/day		

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

84. Vosevi / Proton Pump Inhibitors _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with proton pump inhibitors is not recommended. The solubility of the velpatasvir component of the antiviral combo product is pH dependent and drugs that increase the gastric pH are expected to decrease velpatasvir solubility, and therefore its bioavailability. If concomitant use is considered medically necessary, sofosbuvir/velpatasvir/voxilaprevir can be administered with omeprazole 20 mg. Use with other PPIs has not been studied.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Omeprazole 40 mg	
	Esomeprazole	
	Lansoprazole	
	Dexlansoprazole	
	Rabeprazole	
	Pantoprazole	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

85. Vosevi / Digoxin _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with digoxin, a P-gp substrate, may result in an increase in the plasma concentration of digoxin due to inhibition, by the velpatasvir and voxilaprevir antiviral components, of the P-gp efflux transporter system. Refer to digoxin prescribing information for monitoring and dose modification recommendations.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Digoxin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

86. Vosevi / Tipranavir / Ritonavir _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with ritonavir-boosted tipranavir is not recommended. Tipranavir is a P-gp inducer and co-administration with the P-gp substrates velpatasvir and sofosbuvir has been shown to result in decreased velpatasvir and sofosbuvir plasma concentrations, leading to reduced antiviral efficacy. The effect on voxilaprevir is unknown.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Sofosbuvir/Velpatasvir/Voxilaprevir	Tipranavir	Ritonavir

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

87. Vosevi / Atazanavir & Lopinavir _____ _____

Alert Message: The concurrent user of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with atazanavir- or lopinavir-containing regimens is not recommended. Both atazanavir and lopinavir are OATP1B1 inhibitors and co-administration with the OATP1B1 substrate voxilaprevir may result in increased voxilaprevir plasma concentrations.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Atazanavir Lopinavir	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

88. Vosevi / Tenofovir Disoproxil Fumarate _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with a tenofovir disoproxil fumarate (DF)-containing regimen may result in increased tenofovir DF plasma concentrations and risk for tenofovir-associated adverse reactions. Tenofovir DF is a BCRP and P-gp substrate and the velpatasvir and voxilaprevir components of the antiviral agent inhibit both BCRP- and P-gp-mediated transport.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Tenofovir Disoproxil fumarate - All	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

89. Pravastatin / Vosevi _____ _____

Alert Message: The dose of pravastatin should not exceed 40 mg per day with co-administered with Vosevi (sofosbuvir/velpatasvir/voxilaprevir). The concurrent use of sofosbuvir/velpatasvir/voxilaprevir with pravastatin has been shown to increase pravastatin plasma concentrations which may increase the risk of pravastatin-related myopathy, including rhabdomyolysis. Pravastatin is a OATP1B1/3 substrate and the velpatasvir and voxilaprevir components of the antiviral agent are OATP1B1/3 inhibitors.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Pravastatin 80 mg	Sofosbuvir/Velpatasvir/Voxilaprevir	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

90. Vosevi / Rosuvastatin _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with rosuvastatin is not recommended due to the increased risk of myopathy, including rhabdomyolysis. The velpatasvir and voxilaprevir components of the antiviral agent are inhibitors of BCRP, OATP1B1/3 transporters and concurrent use with rosuvastatin (both a BCRP and OATP1B1/3 substrate) may result in a significant increase in the plasma concentration of rosuvastatin.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Rosuvastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

91. Vosevi / Pitavastatin _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with pitavastatin is not recommended due to increased risk of myopathy, including rhabdomyolysis. The velpatasvir and voxilaprevir component of the antiviral agent are inhibitors or OATP1B1/3 transport and concurrent use with the OAT1B1/3 substrate, pitavastatin, may result in increased pitavastatin plasma concentration.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Pitavastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

92. Vosevi / Atorvastatin _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with atorvastatin may result in increased atorvastatin plasma concentration and risk of myopathy, including rhabdomyolysis. The manufacturer recommends using the lowest approved atorvastatin dose and if higher doses are needed, use the lowest necessary dose based on risk/benefit assessment. Atorvastatin is a substrate of the P-gp and OATP1B1 transporters and the velpatasvir and voxilaprevir components of the antiviral agent are inhibitors of both P-gp and OATP1B1 transporters.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Atorvastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

93. Vosevi / Fluvastatin _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with fluvastatin may result in increased fluvastatin plasma concentration and risk of myopathy, including rhabdomyolysis. The manufacturer recommends using the lowest approved fluvastatin dose and if higher doses are needed, use the lowest necessary dose based on risk/benefit assessment. Fluvastatin is a substrate of OATP1B1 and BCRP transporters and the velpatasvir and voxilaprevir components of the antiviral agent are inhibitors of both OATP1B1 and BCRP transporters.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Fluvastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

94. Vosevi / Lovastatin _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with lovastatin may result in increased lovastatin plasma concentration and risk of myopathy, including rhabdomyolysis. The manufacture recommends using the lowest approved lovastatin dose based on risk/benefit assessment. Lovastatin is a substrate of P-gp and OATP1B1/3 transporters and both the velpatasvir and voxilaprevir components of the antiviral agent are inhibitors pf P-gp and OATP1B1 transporters.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Lovastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.
Kellick KA, Bottorff M, Toth PP. A Clinician's Guide to Statin Drug-Drug Interactions. Jrnl of Clin Lipidol. 2014;8, S30-S46.

95. Vosevi / Simvastatin _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with simvastatin may result in increased simvastatin plasma concentration and risk of myopathy, including rhabdomyolysis. The manufacturer recommends using the lowest approved simvastatin dose based on risk/benefit assessment. Simvastatin is a substrate of P-gp and OATP1B1 transporters and both the velpatasvir and voxilaprevir components of the antiviral agent are inhibitors of P-gp and OATP1B1 transporters.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Simvastatin	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.
Vosevi (sofosbuvir/velpatasvir/voxilaprevir) Drug Approval Package. Clinical Pharmacology and Biopharmaceutics Review(s). Center for Drug Evaluation and Research. App No. 209195Orig1s000. May 8, 2017.
Available at:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209195Orig1s000ClinPharmR.pdf

96. Vosevi / Cyclosporine _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with cyclosporine is not recommended. Co-administration of these agents has been shown to substantially increase the plasma concentration of the voxilaprevir component of the antiviral agent, the safety of which has not been established. Cyclosporine is an OATP transport inhibitor and a voxilaprevir is a substrate of OATP1B1 and OATP1B3.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Cyclosporine	

References:
Clinical Pharmacology, 2017 Elsevier/Gold Standard.
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

97. Vosevi / BCRP Substrates _____ _____

Alert Message: The concurrent use of Vosevi (sofosbuvir/velpatasvir/voxilaprevir) with drugs that are BCRP transporter substrates (e.g., methotrexate, sulfasalazine, and topotecan) is not recommended. Both the velpatasvir and voxilaprevir components of the antiviral agent are inhibitors of BCRP drug transport and co-administration with BCRP substrates may result in increased substrate plasma concentrations.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B	Util C
Sofosbuvir/Velpatasvir/Voxilaprevir	Methotrexate	
	Mitoxantrone	
	Imatinib	
	Irinotecan	
	Lapatinib	
	Sulfasalazine	
	Topotecan	

References:
Vosevi Prescribing Information, Nov. 2017, Gilead Science, Inc.

98. Lesinurad/Allopurinol / CYP3A4 Substrates _____ _____

Alert Message: Concurrent use of Duzallo (lesinurad/allopurinol) with a CYP3A4 substrate (e.g., aprepitant, buspirone, and simvastatin) may result in a decrease in systemic exposure and therapeutic effect of the CYP3A4 substrate. The lesinurad component of the combo product is a weak CYP3A4 inducer. The manufacturer recommended monitoring the patient for potential reduction in CYP3A substrate efficacy when co-administered with lesinurad.

Conflict Code: DD – Drug/Drug Interaction
Drugs/Diseases

Util A	Util B			Util C
Lesinurad/Allopurinol	Quinidine	Budesonide	Ticagrelor	
	Amiodarone	Eplerenone	Apixaban	
	Ivabradine	Tolvaptan	Aprepitant	
	Eletriptan	Ifosfamide	Olaparib	
	Sildenafil	Vinblastine	Quetiapine	
	Tadalafil	Vincristine	Palbociclib	
	Vardenafil	Vinorelbine	Lurasidone	
	Avanafil	Etoposide	Dapsone	
	Isradipine	Docetaxel	Solifenacin	
	Felodipine	Abiraterone	Atazanavir	
	Amlodipine	Imatinib	Alfuzosin	
	Disulfiram	Bortezomib	Bedaquiline	
	Eszopiclone	Erlotinib	Silodosin	
	Flurazepam	Sunitinib	Tacrolimus	
	Alprazolam	Dasatinib	Simvastatin	
	Triazolam	Lapatinib	Tofacitinib	
	Midazolam	Nilotinib	Lovastatin	
	Buspirone	Pazopanib	Cilostazol	
	Quazepam	Vandetanib		
	Vilazodone	Crizotinib		
	Hydrocodone	Axitinib		
	Oxycodone	Bosutinib		
	Buprenorphine	Cabozantinib		
	Ethosuximide	Ibrutinib		
	Clonazepam	Ceritinib		
	Tiagabine	Irinotecan		

References:
Duzallo Prescribing Information, Aug. 2017, Ironwood Pharmaceuticals, Inc.
Clinical Pharmacology, 2017, Elsevier/Gold Standard.