DUR Board Meeting
March 4, 2015
North Dakota Heritage Center

North Dakota Medicaid
DUR Board Meeting Agenda
North Dakota Heritage Center
612 East Boulevard Avenue
Bismarck, ND
March 4, 2015
1pm

1. Administrative items
    - Travel vouchers
    - Introduction of new members

2. Old business
    - Review and approval of minutes of 12/14 meeting — Chair
    - Budget update — Brendan

3. New business
    - Review of Otezla — HID
    - Review of Xtoro — HID
    - Review of Hemangeol — HID
    - Review of Lemtrada — HID
    - Review of agents used to treat idiopathic pulmonary fibrosis (Ofev, Esbriet) — HID
    - Review of GLP-1 receptor agonists — HID
    - Review of topical therapies for onychomycosis — HID
    - Criteria recommendations — HID
    - Upcoming meeting date/agenda — Chair

4. Adjourn — Chair

Please remember to silence all cellular phones during the meeting.

Drug Utilization Review (DUR) Meeting Minutes
December 3, 2014

Members Present: John Savageau, Jeffrey Hostetter, Peter Woodrow, Russ Sobotta, Tanya Schmidt, Steve Irsfeld, Michael Booth, Carlotta McCleary, Laura Schield, Katie Kram, Wendy Brown, Emmet Kenney

Members Absent: James Carlson, Leann Ness

Medicaid Pharmacy Department: Brendan Joyce

J. Savageau called the meeting to order at 1:00 p.m. Chair J. Savageau asked for a motion to approve the minutes from the September meeting. J. Hostetter moved that the minutes be approved, and P. Woodrow seconded the motion. Chair J. Savageau called for a voice vote to approve the minutes. The motion passed with no audible dissent.

Updated AAP guidelines for palivizumab prophylaxis
B. Joyce discussed the updated guidelines for palivizumab (Synagis) and the Board watched the American Academy of Pediatrics webinar providing a summary of the recommendations. The Board voted to accept the updated guidelines at the September meeting and asked that data be brought back in December showing how many children during the 2013-2014 Synagis season would not have received medication. The Board reviewed the data provided. Dr. Rafeal Ocejo, a pediatrician in Bismarck, spoke regarding the new guidelines. Dr. Joan Connell, a pediatrician in Bismark, spoke regarding the new guidelines. A. Bandell, representing MedImmune, spoke regarding Synagis. A motion was made by J. Hostetter to continue using the new guidelines and include patients 29 weeks – 31weeks and 6 days gestational age. K. Kram seconded the motion. Chair J. Savageau called for a voice vote. The motion passed with no audible dissent. All PA requests that do not meet AAP guidelines will be reviewed on a case-by-case basis.

Benzodiazepine review
B. Joyce reviewed benzodiazepine utilization with the Board. Data regarding duplicate therapy, top prescribers, top diagnoses, and age ranges of patients was shared. A recommendation was made to limit duplicate benzodiazepine therapy to one short-acting product and one long-acting product. Quantity limits may also be implemented.

Second reviews
A motion and second were made at the September meeting to place topical testosterone products, phosphate binders, Zontivity, and Evzio on prior authorization. The topics were brought up for a second review. There was no public comment. After discussion, Chair J. Savageau called for a voice vote to approve the motion. The motion passed with no audible dissent.

Yearly PA review
The Board reviews products annually that have previously been placed on prior authorization, which allows the Board a chance to update the prior authorization forms and criteria. All forms and criteria were reviewed. Changes suggested:

1. Buprenorphine form-add ‘to the best of my knowledge’ at the beginning of the check box that says ‘patient is not taking other opioids, tramadol, or carisoprodol concurrently with buprenorphine containing products.'
2. Remove Cozaar from the ARB form.
3. Make sure all new products are on the COPD form.

J. Howard, representing Mylan, spoke regarding Epi-Pen.

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, new warnings, etc. These proposed criteria will be added to the current set of criteria and will be used in future DUR cycles. P. Woodrow moved to approve the new criteria and W. Brown seconded the motion. Chair J. Savageau called for a voice vote. The motion passed with no audible dissent.

The next DUR Board meeting will be held March 4 in Bismarck. J. Hostetter made a motion to adjourn the meeting. W. Brown seconded. The motion passed with no audible dissent. J. Savageau adjourned the meeting.

PRODUCT DETAILS OF OTEZLO (APREMILAST)

INDICATIONS AND USE: Otezla is an inhibitor of phosphodiesterase 4 (PDE4) and is indicated for the treatment of adult patients with active psoriatic arthritis and patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

DOSAGE FORMS: Otezla is available as 10 mg, 20 mg, and 30 mg tablets.

DOSAGE AND ADMINISTRATION: To reduce the risk of gastrointestinal symptoms, titrate to a recommended dose of 30 mg twice daily according to the following schedule:

- Day 1: 10 mg in the morning
- Day 2: 10 mg in the morning and 10 mg in the evening
- Day 3: 10 mg in the morning and 20 mg in the evening
- Day 4: 20 mg in the morning and 20 mg in the evening
- Day 5: 20 mg in the morning and 30 mg in the evening
- Day 6 and thereafter: 30 mg twice daily
- Otezla dosage should be reduced to 30 mg once daily in patients with severe renal impairment.

SPECIAL POPULATIONS:

- Otezla is classified as pregnancy category C. There are no adequate and well-controlled studies of Otezla in pregnant women.
- Because many drugs are present in human milk, caution should be exercised when Otezla is administered to a nursing woman.
- The safety and effectiveness of Otezla in pediatric patients less than 18 years of age have not been established.
- No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

WARNINGS AND PRECAUTIONS:

- Treatment with Otezla is associated with an increase in adverse reactions of depression. Before using Otezla in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with Otezla in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts, or other mood changes.
- During the controlled period of the studies, weight decrease between 5-10% of body weight was reported in 10% of patients compared to 3.3% treated with placebo. Patients treated with Otezla should have their weight monitored regularly.
- Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of Otezla. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with Otezla is not recommended.

ADVERSE REACTIONS:

- Psoriatic Arthritis: The most common adverse reactions (≥5%) are diarrhea, nausea, and headache.
- Psoriasis: The most common adverse reactions (≥5%) are diarrhea, nausea, upper respiratory tract infection, and headache, including tension headache.

PATIENT COUNSELING INFORMATION:

- Before using Otezla in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risk and benefits of treatment.
- Be alert for the emergence or worsening of depression, suicidal thoughts, or other mood changes, and if such changes occur, contact their healthcare provider.
- Patients treated with Otezla should have their weight monitored regularly.
- The use of strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with Otezla is not recommended.
- Otezla can be taken with or without food.
- Tablets should not be crushed, split, or chewed.

References:

1. Otezla [package insert]. Summit, NJ: Celgene Corporation; September 2014.

PRODUCT DETAILS OF XTORO (FINAFLOXACIN OTIC SUSPENSION)

INDICATIONS AND USE: Xtoro is a quinolone antimicrobial indicated for the treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus.*

DOSAGE FORMS: Xtoro is available as 5 mL of finafloxacin otic suspension 0.3%.

ADMINISTRATION: Instill four drops in the affected ear(s) twice daily for seven days. For patients requiring use of an otowick, the initial dose can be doubled (to 8 drops) by 4 drops instilled into the affected ear twice daily for seven days.

WARNINGS AND PRECAUTIONS:

- Prolonged use of this product may lead to overgrowth of nonsusceptible organisms. Discontinue use if this occurs.
- Allergic reactions may occur in patients with a history of hypersensitivity to finafloxacin, to other quinolones, or to any of the components in this medication. Discontinue use if this occurs.

USE IN SPECIFIC POPULATIONS:

- Pregnancy category C. Xtoro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Caution should be exercised when finafloxacin is administered to a nursing mother.
- The safety and efficacy of Xtoro in infants below one year of age have not been established.

ADVERSE REACTIONS: The most common adverse reactions occurring in 1% of patients with Xtoro were ear pruritus and nausea.

PATIENT COUNSELING INFORMATION:

- If a rash or allergic reaction occurs, discontinue the use of Xtoro and contact physician.
- Warm the bottle in hands before use to avoid dizziness which may result from the instillation of a cold solution.
- When using with otowick, instill 8 drops at the time of otowick insertion, then continue with 4 drops administered twice daily for 7 days.

References:

1. Xtoro [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; November 2014.

PRODUCT DETAILS OF HEMANGEOL (PROPRANOLOL HYDROCHLORIDE ORAL SOLUTION)

INDICATIONS AND USE: Hemangeol oral solution is a beta-adrenergic blocker indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.

DOSAGE FORMS: Oral solution: 4.28 mg/mL propranolol hydrochloride.

ADMINISTRATION:

- Initiate treatment at ages 5 weeks to 5 months.
- Starting dose is 0.15 mL/kg (0.6 mg/kg) twice daily. After 1 week, increase dose to 0.3 mL/kg (1.1 mg/kg) twice daily. After 2 weeks, increase to a maintenance dose of 0.4 mL/kg (1.7 mg/kg) twice daily.
- Administer doses at least 9 hours apart during or after feeding.
- Readjust dose for changes in the child's weight.
- Monitor heart rate and blood pressure for 2 hours after first dose or increasing dose.

WARNINGS AND PRECAUTIONS:

- Hypoglycemia: administer during or after feeding. Do not use in patients who are not able to feed or are vomiting.
- Bradycardia and hypotension.
- Bronchospasm: avoid use in patients with asthma or lower respiratory infection.
- Increased risk of stroke in PHACE syndrome.

USE IN SPECIFIC POPULATIONS:

- Pregnancy category C. Hemangeol is not intended to be prescribed to pregnant women.
- Hemangeol is not intended to be prescribed to breastfeeding women.
- The safety and effectiveness for infantile hemangioma have not been established in pediatric patients greater than 1 year of age.

ADVERSE REACTIONS: The most common adverse reactions occurring in ≥ 10% of patients were sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting.

PATIENT COUNSELING INFORMATION:

- There is a risk of hypoglycemia when given to infants who are not feeding regularly or who are vomiting. Skip dosing under such conditions.
- There is a potential risk for bradycardia, aggravation of pre-existing conduction disorders, and hypotension. Contact a healthcare provider in case of fatigue, pallor, slow or uneven heart beats, peripheral coldness, or fainting.
- There is a risk of bronchospasm or exacerbation of lower respiratory tract infections. Contact a healthcare provider or go to the nearest hospital emergency room if there are breathing problems or wheezing during treatment.
- Changes in sleep patterns may occur.

References:

1. Hemangeol [package insert]. Parsippany, NJ: Pierre Fabre Pharmaceuticals, Inc.; March 2014.

PRODUCT DETAILS OF LEMTRADA (ALEMTUZUMAB)

INDICATIONS AND USE: Lemtrada is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

DOSAGE FORMS: Injection: 12 mg/1.2 mL (10 mg/mL) in a single-use vial.

ADMINISTRATION:

- Administer by intravenous infusion over 4 hours for 2 treatment courses.
- Premedicate with corticosteroids prior to infusion for the first 3 days of each treatment course.
- Administer antiviral agents for herpetic prophylaxis starting on the first day dosing and continuing for a minimum of two months after completion of dosing or until CD4+ lymphocyte count is more than 200 cells per microliter, whichever occurs later.

WARNINGS AND PRECAUTIONS:

- Thyroid disorders: obtain thyroid function tests prior to initiation of treatment and every 3 months until 48 months after the last infusion.
- Monitor complete blood counts monthly until 48 months after the last infusion.
- Consider delaying initiation in patients with active infections until the infection is fully controlled. Do not administer live viral vaccines following a course of therapy.

USE IN SPECIFIC POPULATIONS:

- Pregnancy category C. Lemtrada should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- The safety and effectiveness in pediatric patients less than 17 years of age have not been established.

ADVERSE REACTIONS: The most common adverse reactions occurring in ≥ 10% of patients and > interferon beta-1a: rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting.

PATIENT COUNSELING INFORMATION:

- Advise patients to contact their healthcare provider promptly if they experience any symptoms of potential autoimmune disease.
- Advise patients of the importance of monthly blood and urine tests for 48 months following the last course of therapy for signs of autoimmunity.
- Lemtrada may cause hyperthyroid or hypothyroid disorders.
- Infusion reactions can occur.
- Lemtrada may increase the risk of malignancies including thyroid cancer and melanoma.
- Advise patients to contact their healthcare provider if they develop symptoms of serious infections such as fever or swollen glands.
- Advise patients that pneumonitis has been reported.

References:

1. Lemtrada [package insert]. Cambridge, MA: Genzyme Corporation; November 2014.

PRODUCT DETAILS OF AGENTS USED TO TREAT IDIOPATHIC PULMONARY FIBROSIS

INDICATIONS AND USE:

Drug	Indication
Ofev (nintedanib)	Ofev is a kinase inhibitor indicated for the treatment of idiopathic pulmonary fibrosis (IPF).
Esbriet (pirfenidone)	Esbriet is a pyridone indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

COMPARISON:

Drug	Dose	Approximate Cost
Ofev (nintedanib)	150 mg twice daily approximately 12 hours apart	$144/capsule
Esbriet (pirfenidone)	801 mg (three capsules) three times daily taken with food	$31/capsule

HOW SUPPLIED:

Drug	How supplied
Ofev (nintedanib)	150 mg and 100 mg capsules
Esbriet (pirfenidone)	267 mg capsules

WARNINGS AND PRECAUTIONS:

Drug	Warnings and Precautions
Ofev (nintedanib)	• Elevated liver enzymes • Gastrointestinal disorders • Embryofetal toxicity • Arterial thromboembolic events
Esbriet (pirfenidone)	• Elevated liver enzymes • Photosensitivity and rash • Gastrointestinal disorders

ADVERSE REACTIONS:

Drug	Adverse Reactions
Ofev (nintedanib)	• The most common adverse reactions (incidence ≥5%) are diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased, and hypertension.
Esbriet (pirfenidone)	• The most common adverse reactions (incidence ≥10%) are nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastro-esophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

DRUG INTERACTIONS:

Drug	Drug Interactions
Ofev (nintedanib)	Coadministration of P-gp and CYP3A4 inhibitors may increase nintedanib exposure. Monitor patients closely for tolerability of Ofev.
Esbriet (pirfenidone)	Moderate (e.g., ciprofloxacin) and strong inhibitors of CYP1A2 (e.g., fluvoxamine) increase systemic exposure of Esbriet and may alter the adverse reaction profile of Esbriet. Discontinue fluvoxamine prior to administration of Esbriet or reduce to one capsule three times a day. Consider dosage reduction with use of ciprofloxacin.

References:

1. Ofev [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2014.
2. Esbriet [package insert]. Brisbane, CA: InterMune, Inc.; October 2014.

PRODUCT DETAILS OF GLP-1 AGONISTS (GLUCAGON-LIKE PEPTIDE-1)

INDICATIONS AND USE: GLP-1 receptor agonists are indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. These agents should not be used as initial monotherapy. For most patients, GLP-1 agonists should be reserved for those who require two or more diabetes medications to maintain a desired A1C.

COMPARISON:

GLP-1 Agonist	~ A1C Decrease	~ Weight Loss	~ Cost/month	Dosing Frequency
Byetta (exenatide)	1%	4 lbs	$430	Twice daily
Bydureon (exenatide ER)	1.5%	6 lbs	$440	Once weekly
Tanzeum (albiglutide)	1%	2 lbs	$330	Once weekly
Trulicity (dulaglutide)	1.5%	6 lbs	$500	Once weekly
Victoza (liraglutide)	1.5%	6 lbs	$400-600	Once daily

HOW SUPPLIED:

GLP-1 Agonist	Package Size
Byetta (exenatide)	5 mcg per dose, 60 doses (1.2 mL prefilled pen). 10 mcg per dose, 60 doses (2.4 mL prefilled pen).
Bydureon (exenatide ER)	Single-dose tray containing 2 mg vial. Single-dose 2 mg pen.
Tanzeum (albiglutide)	30 mg single-dose pen and 50 mg single-dose pen (carton of 4).
Trulicity (dulaglutide)	Carton of 4 single-dose pen or prefilled syringe: (0.75 mg/0.5 mL and 1.5 mg/0.5 mL).
Victoza (liraglutide)	Disposable, pre-filled, multi-dose pens delivering doses of 0.6mg, 1.2mg, or 1.8mg (6 mg/mL, 3mL).

DOSAGE AND ADMINISTRATION:

GLP-1 Agonist	Dosage and Administration
Byetta (exenatide)	• Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). • Initiate at 5 mcg per dose twice daily; increase to 10 mcg twice daily after 1 month based on clinical response.
Bydureon (exenatide ER)	• Administer 2 mg by subcutaneous injection once every seven days (weekly), at any time of day and with or without meals. • Administer immediately after the dose is prepared.
Tanzeum (albiglutide)	• Administer once weekly at any time of day, without regard to meals. • Inject subcutaneously in the abdomen, thigh, or upper arm. • Initiate at 30 mg subcutaneously once weekly. Dose can be increased to 50 mg once weekly in patients requiring additional glycemic control. • If a dose is missed, administer within 3 days of missed dose.
Trulicity (dulaglutide)	• Administer once weekly at any time of day. • Inject subcutaneously in the abdomen, thigh, or upper arm. • Initiate at 0.75 mg subcutaneously once weekly. Dose can be increased to 1.5 mg once weekly for additional glycemic control. • If a dose is missed, administer within 3 days of missed dose.

GLP-1 Agonist	Dosage and Administration
Victoza (liraglutide)	• Administer once daily at any time of day, independently of meals. • Inject subcutaneously in the abdomen, thigh or upper arm. • The injection site and timing can be changed without dose adjustment. • Initiate at 0.6 mg per day for one week. This dose is intended to reduce gastrointestinal symptoms during initial titration and is not effective for glycemic control. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg.

SPECIAL POPULATIONS:

GLP-1 Agonist	Special Populations
Byetta (exenatide)	• Byetta should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. • Caution should be exercised when Byetta is administered to a nursing woman.
Bydureon (exenatide ER)	• Bydureon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. • Caution should be exercised when Bydureon is administered to a nursing woman.
Tanzeum (albiglutide)	• Tanzeum should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. • Discontinue nursing or discontinue Tanzeum. • Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.
Trulicity (dulaglutide)	• Trulicity should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. • Discontinue nursing or discontinue Trulicity. • Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.
Victoza (liraglutide)	• Victoza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. • Discontinue nursing or discontinue Victoza.

WARNINGS AND PRECAUTIONS:

GLP-1 Agonist	Warnings and Precautions
Byetta (exenatide)	• Never share a Byetta pen between patients, even if the needle is changed. • Postmarketing reports with Byetta include fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly. Consider other antidiabetic therapies in patients with a history of pancreatitis. • Increased risk of hypoglycemia when used in combination with medications known to cause hypoglycemia (e.g., insulin or insulin secretagogue). Consider reducing the dose of insulin or insulin secretagogue. • Byetta should not be used in patients with severe renal impairment or end-stage renal disease and should be used with caution in patients with renal transplantation. Caution should be applied when initiating Byetta in patients with moderate renal failure.

GLP-1 Agonist	Warnings and Precautions
	• Use of Byetta is not recommended in patients with severe gastrointestinal disease. • Patient should discontinue Byetta if symptoms of hypersensitivity reactions (e.g., anaphylaxis and angioedema) arise.
Bydureon (exenatide ER)	• Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors. • Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • Increased risk of hypoglycemia when Bydureon is used in combination with a sulfonylurea. Consider reducing the sulfonylurea dose. • Not recommended if patient has severe renal impairment or end-stage renal disease. Use with caution in patients with renal-transplantation or moderate renal impairment. • Not recommended in patients with severe gastrointestinal disease. • Patient should discontinue Bydureon if symptoms of hypersensitivity reactions (e.g., anaphylaxis and angioedema) arise.
Tanzeum (albiglutide)	• Discontinue promptly if pancreatitis is suspected. Do not restart if confirmed. • Hypoglycemia can occur when used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Consider lowering sulfonylurea or insulin dosage when starting Tanzeum. • Discontinue Tanzeum if hypersensitivity reactions are suspected. • Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.
Trulicity (dulaglutide)	• Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors. • Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • Increased risk of hypoglycemia when Trulicity is used with an insulin secretagogue or insulin. Consider lowering the dose of sulfonylurea or insulin to reduce the risk. • Discontinue Trulicity if hypersensitivity reactions are suspected. • Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.
Victoza (liraglutide)	• Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors. • Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. • Increased risk of hypoglycemia when Victoza is used with an insulin secretagogue or insulin. Consider lowering the dose of the insulin secretagogue or insulin to reduce the risk. • Use caution when initiating or escalating doses of Victoza in patients with renal impairment. • Discontinue Victoza if hypersensitivity reactions are suspected.

ADVERSE REACTIONS:

GLP-1 Agonist	Adverse Reactions
Byetta (exenatide)	• Most common (≥ 5%) and occurring more frequently than placebo in clinical trials: nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, constipation, and asthenia. • Postmarketing reports with exenatide of increased international normalized ratio (INR) with concomitant use of warfarin, sometimes with bleeding.
Bydureon (exenatide ER)	• Most common (≥ 5%) and occurring more frequently than comparator in clinical trials: nausea, diarrhea, headache, vomiting, constipation, injection-site pruritus, injection-site nodule, and dyspepsia.
Tanzeum (albiglutide)	• Adverse reactions, reported in ≥ 10% of patients and more frequently than in patients on placebo, were upper respiratory tract infection, diarrhea, nausea, and injection site reaction.
Trulicity (dulaglutide)	• The most common adverse reactions, reported in ≥ 5% of patients are nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.
Victoza (liraglutide)	• The most common adverse reactions, reported in ≥ 5% of patients and occurring more frequently than in patients treated with placebo, were headache, nausea, diarrhea, and anti-liraglutide antibody formation. • Immunogenicity-related events, including urticaria, were more common among Victoza-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

UTILIZATION:

ND Medicaid GLP-1 Utilization			
12/30/13 – 12/29/14			
Label Name	**Rx Num**	**Total Reimb Amt**	**Avg Cost per Script**
Byetta 5 mcg Dose Pen	12	$4,562.62	$380.22
Byetta 10 mcg Dose Pen	71	$31,548.67	$444.35
Bydureon 2 mg Pen	1	$342.00	$342.00
Bydureon 2 mg Vial	43	$18,891.45	$439.34
Victoza 2-Pak	159	$60,963.42	$383.42
Victoza 3-Pak	144	$81,081.70	$563.07
Total (87 recipients)	430	$197,389.86	

References:

1. PL Detail-Document, Comparison of GLP-1 Agonists. Pharmacist's Letter/Prescriber's Letter. December 2014.
2. Byetta [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2014.
3. Bydureon [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2015.
4. Tanzeum [package insert]. Research Triangle Park, NC: GlaxoSmithKline LLC; June 2014.
5. Trulicity [package insert]. Indianapolis, IN: Eli Lilly and Company; December 2014.
6. Victoza [package insert]. Plainsboro, NY: Novo Nordisk Inc.; July 2013.

PRODUCT DETAILS OF NEW TOPICAL THERAPIES FOR ONYCHOMYCOSIS

INDICATIONS AND USE:

Jublia (efinaconazole)	Topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes.*
Kerydin (tavaborole)	Topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes.*

COMPARISON:

Drug	Dose	Efficacy	~ Cost	Comments
Jublia (efinaconazole)	Apply to affected toenails once daily for 48 weeks.	Toenail complete cure rate 17% at week 52.	$450/4 mL	Consider for patients who can't use oral therapy.
Kerydin (tavaborole)	Apply to affected toenails once daily for 48 weeks.	Toenail complete cure rate < 10% at week 52.	$450/4 mL	Consider for patients who can't use oral therapy.

HOW SUPPLIED:

Jublia (efinaconazole)	4 mL and 8 mL 10% topical solution
Kerydin (tavaborole)	4 mL and 10 mL 5% topical solution

ADVERSE REACTIONS:

Drug	Adverse Reactions
Jublia	• The most common adverse reactions (incidence >1%) were ingrown toenails, application site dermatitis, application site vesicles, and application site pain.
Kerydin	• Common adverse reactions occurring in ≥1% in subjects included application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis.

References:

1. PL Detail-Document, Comparison of Topical Therapies for Onychomycosis. Pharmacist's Letter/Prescriber's Letter. July 2014.
2. Jublia [package insert]. Bridgewater, NY: Valeant Pharmaceuticals North America, LLC; June 2014.
3. Kerydin [package insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; July 2014.

NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
4TH QUARTER 2014

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

1. Suvorexant / Overutilization _____ _____

Alert Message: The manufacturer's recommended dose of Belsomra (suvorexant) is 10 mg, taken no more than once per night and within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening. If 10 mg is well-tolerated but not effective, the dose can be increased to a maximum of 20 mg once daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Suvorexant		

Max Dose: 20 mg/day

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

2. Suvorexant / Narcolepsy _____ _____

Alert Message: Belsomra (suvorexant) is contraindicated in patients with narcolepsy. Suvorexant is an orexin receptor antagonist and this mechanism of action may account for the ability of suvorexant to produce signs of narcolepsy/cataplexy.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Suvorexant		Narcolepsy

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

3. Suvorexant / Respiratory Disease _____ _____

Alert Message: Caution should be exercised when prescribing Belsomra (suvorexant) to patients with compromised respiratory function due to the potential of suvorexant-induced respiratory depression.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Suvorexant		Asthma
		COPD
		Emphysema
		Bronchitis
		Obstructive Sleep Apnea

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

4. Suvorexant / Depression & Suicidal Thinking _____ _____

Alert Message: Belsomra (suvorexant) should be used with caution in patients with depression or suicidal ideation. In clinical studies, a dose-dependent increase in suicidal ideation was observed in patients taking suvorexant, as assessed by questionnaire. In primarily depressed patients, sedative/hypnotic use has been associated with worsening depression and suicidal thoughts and actions. The lowest number of tablets that is feasible should be prescribed for the patient at any one time.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Suvorexant		Depression
		Suicide
		Suicidal Ideation

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

5. Suvorexant / Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations Cataplexy-like Symptoms _____ _____

Alert Message: Sleep paralysis, hypnagogic/hypnopompic hallucinations, and symptoms similar to cataplexy can occur with Belsomra (suvorexant) use, and the risk of occurrence may increase with dose. Patient should be informed of the nature of these events when prescribed suvorexant.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Suvorexant		

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

6. Suvorexant / CNS Depressants _____ _____

Alert Message: Concurrent use of Belsomra (suvorexant) with a CNS depressant may require dosage adjustment of suvorexant and/or the other drug due to the potential for additive depressant effects.

Conflict Code:
Drugs/Diseases

Util A	Util B	Util C
Suvorexant	Antidepressants	
	Opioid Agonists & Mixed Agonist/Antagonist	
	Barbiturates	
	Phenothiazines	
	Anxiolytics	
	Anticonvulsants	
	Antipsychotics	
	Sedating Antihistamines	
	Muscle Relaxants	
	Antiparkinson Agents (Dopaminergic & COMT)	
	Sedative/Hypnotics	

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

7. Suvorexant / Strong CYP3A4 Inhibitors _____ _____

Alert Message: Concurrent use of Belsomra (suvorexant) with a strong CYP3A4 inhibitor is not recommended. Suvorexant is primarily metabolized by CYP3A4 and inhibition of this isoenzyme may significantly increase suvorexant exposure and increase the risk of suvorexant adverse effects.

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

Util A	Util B		Util C
Suvorexant	Nefazodone	Ketoconazole	
	Clarithromycin	Itraconazole	
	Telithromycin	Posaconazole	
	Saquinavir	Voriconazole	
	Ritonavir	Boceprevir	
	Nelfinavir	Telaprevir	
	Indinavir		

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
FDA US Food and Drug Administration: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

8. Suvorexant / Moderate CYP3A4 Inhibitors _____ _____

Alert Message: The recommended dose of Belsomra (suvorexant) is 5 mg in patients receiving a moderate CYP3A4 inhibitor but may be increased to a maximum of 10 mg in these patients if necessary for efficacy. Suvorexant is primarily metabolized by CYP3A4 and inhibition of this isoenzyme may significantly increase suvorexant exposure and increase the risk of suvorexant-related adverse effects.

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

Util A	Util B		Util C
Suvorexant 20 mg	Aprepitant	Fluconazole	
	Atazanavir	Fosamprenavir	
	Ciprofloxacin	Imatinib	
	Diltiazem	Verapamil	
	Erythromycin		

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
FDA US Food and Drug Administration: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

9. Suvorexant / Strong CYP3A4 Inducer _____ _____

Alert Message: The concurrent use of Belsomra (suvorexant) and a strong CYP3A4inducer may result in reduced suvorexant efficacy due to induction of suvorexant CYP3A4-mediated metabolism.

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

Util A	Util B	Util C
Suvorexant	Carbamazepine	
	Phenytoin	
	Phenobarbital	
	Primidone	
	Rifampin	
	Efavirenz	

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
FDA US Food and Drug Administration: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Accessed: 08/230/2012.
Available at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

10. Suvorexant / Digoxin _____ _____

Alert Message: The concurrent use of Belsomra (suvorexant) with digoxin has been shown to slightly increase digoxin levels due to inhibition of intestinal P-glycoprotein (P-gp). Digoxin concentrations should be monitored when co-administering suvorexant with digoxin.

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

Util A	Util B	Util C
Suvorexant	Digoxin	

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

11. Suvorexant / Pediatric Use _____ _____

Alert Message: The safety and effectiveness of Belsomra (suvorexant) have not been established in pediatric patients.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Suvorexant		

Age Range: 0 -18 yoa

References:
Belsomra Prescribing Information, August 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.

12. Arformoterol / Overutilization _____ _____

Alert Message: Brovana (arformoterol) may be over-utilized. The manufacturer's recommended maximum dose is 30 mcg per day (15 mcg twice daily). Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta-2 adrenergic drugs, do not use arformoterol more often, at higher doses than recommended, or with other long-acting beta agonists.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Arformoterol		

Max Dose: 30 mcg/day

References:
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.
Brovana Prescribing Information, Feb. 2014, Sunovion Pharmaceuticals, Inc.

13. Arformoterol / Hepatic Impairment _____ _____

Alert Message: Brovana (arformoterol) should be used cautiously in patients with hepatic impairment. Systemic exposure (Cmax & AUC) to arformoterol increased 1.3 to 2.4-fold in subjects with hepatic impairment as compared to matched healthy control subjects. While dosage adjustment is not required, it is recommended that these patients be monitored closely.
Conflict Code: MC – Drug (Actual) Disease Precaution
Drugs/Disease:

Util A	Util B	Util C
Arformoterol	Hepatic Impairment	

References:
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.
Brovana Prescribing Information, Feb. 2014, Sunovion Pharmaceuticals, Inc.

14. Arformoterol / Therapeutic Appropriateness _____ _____

Alert Message: Brovana (arformoterol) should not be used in children as the safety and efficacy of arformoterol have not been established in pediatric patients.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Disease:

Util A	Util B	Util C
Arformoterol		

Age Range: 0 – 18 years of age

References:
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.
Brovana Prescribing Information, Feb. 2014, Sunovion Pharmaceuticals, Inc.

15. Arformoterol / MOAIs & TCAs & QT Prolongation _____ _____

Alert Message: Brovana (arformoterol), as well as other beta 2-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval. Concurrent use of these agents may potentiate the adrenergic agonist action of arformoterol on the cardiovascular system.

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

Util A	Util B		Util C		
Arformoterol	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	Rasagiline
	Clomipramine	Gemifloxacin	Octreotide	Sunitinib	
	Clozapine	Granisetron	Ofloxacin	Tacrolimus	
	Dasatinib	Haloperidol	Ondansetron	Tamoxifen	
	Desipramine	Ibutilide	Paliperidone	Telithromycin	
	Diphenhydramine	Iloperidone	Paroxetine	Terbutaline	

References:
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.
Brovana Prescribing Information, Feb. 2014, Sunovion Pharmaceuticals, Inc.

16. Arformoterol / Beta-Blockers _____ _____

Alert Message: The concurrent use of Brovana (arformoterol) and a beta-adrenergic receptor blocker may result in antagonism. The beta blocker may block the therapeutic effect of the beta-agonist as well as produce severe bronchospasms in COPD patients.

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

Util A	Util B		Util C
Arformoterol	Atenolol	Metoprolol	
	Betaxolol	Timolol	
	Penbutolol	Sotalol	
	Carteolol	Acebutolol	
	Bisoprolol	Propranolol	
	Pindolol	Timolol	

References:
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.
Brovana Prescribing Information, Feb. 2014, Sunovion Pharmaceuticals, Inc.

17. Arformoterol / Methylxanthines & Steroids & K+ Depleting Diuretics _____ _____

Alert Message: The concurrent use of Brovana (arformoterol) with methylxanthines (theophylline, aminophylline), steroids, or potassium depleting diuretics may potentiate any hypokalemic effect of arformoterol. Monitor patients for development of hypokalemia.

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

Util A	Util B		Util C
Arformoterol	Theophylline	Budesonide	Chlorothiazide
	Aminophylline	Betamethasone	Hydrochlorothiazide
	Prednisone	Triamcinolone	Bendroflumethiazide
	Prednisolone	Furosemide	Methyclothiazide
	Hydrocortisone	Bumetanide	Indapamide
	Cortisone	Torsemide	Metolazone
	Dexamethasone	Ethacrynic Acid	Chlorthalidone
	Methylprednisolone		

References:
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.
Brovana Prescribing Information, Feb. 2014, Sunovion Pharmaceuticals, Inc.

18. Arformoterol / Therapeutic Appropriateness (Black Box Warning) _____ _____

Alert Message: Brovana (arformoterol) is a long-acting beta-2-adrenergic agonist (LABA) and all LABAs increase the risk of asthma-related death. The safety and efficacy of arformoterol in patients with asthma have not been established. Arformoterol is not indicated for the treatment of asthma.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Indacaterol		

References:
Brovana Prescribing Information, Feb. 2014, Sunovion Pharmaceuticals, Inc.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

19. Arformoterol / Non-adherence _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Brovana (arformoterol). 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: LR – Non-adherence
Drugs/Diseases

Util A	Util B	Util C
Arformoterol		

References:
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 COPD. 2010 Nov 24;5:401-406.

20. Olodaterol / Overutilization _____ _____

Alert Message: The manufacturer's recommended dose of Striverdi Respimat (olodaterol) is 2 inhalations once-daily. Do not use olodaterol inhalation more than two inhalations every 24 hours. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Olodaterol		

Max Dose: 2 inhalations per day = (5.0 mcg olodaterol/day)

References:
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Striverdi Respimat Prescribing Information, July 2014, Boehringer Ingelheim Pharmaceuticals, Inc.

21. Olodaterol / Black Box Warning _____ _____

Alert Message: Striverdi Respimat (olodaterol) is a long-acting beta-2 adrenergic agonist (LABA) and all LABAs increase the risk of asthma-related death. The safety and efficacy of olodaterol in patients with asthma have not been established. Olodaterol is not indicated for the treatment of asthma.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Olodaterol		

References:
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Striverdi Respimat Prescribing Information, July 2014, Boehringer Ingelheim Pharmaceuticals, Inc.

22. Olodaterol / Cardiovascular, Convulsive Disorders, Diabetes & Thyrotoxicosis _____ _____

Alert Message: Striverdi Respimat (olodaterol) should be used with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, or sensitivity to sympathomimetic drugs. Olodaterol is a sympathomimetic amine and can exacerbate these conditions.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Olodaterol	Hypertension	
	Arrhythmias	
	Heart Failure	
	Diabetes	
	Seizures	
	Epilepsy	

References:
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Striverdi Respimat Prescribing Information, July 2014, Boehringer Ingelheim Pharmaceuticals, Inc.

23. Olodaterol / MAOIs, TCAs & Other QTc Prolonging Meds _____ _____

Alert Message: Striverdi Respimat (olodaterol) should be administered with extreme caution to patients being treated with MAOIs, TCAs, or drugs known to prolong the QTc interval because the action of the adrenergic agonist, olodaterol, on the cardiovascular system may be potentiated by these agents.

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

Util A	Util B				Util C
Olodaterol	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	Rasagiline
	Clomipramine	Gemifloxacin	Octreotide	Sunitinib	
	Clozapine	Granisetron	Ofloxacin	Tacrolimus	
	Dasatinib	Haloperidol	Ondansetron	Tamoxifen	
	Desipramine	Ibutilide	Paliperidone	Telithromycin	
	Diphenhydramine	Iloperidone	Paroxetine	Terbutaline	

References:
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Striverdi Respimat Prescribing Information, July 2014, Boehringer Ingelheim Pharmaceuticals, Inc.

24. Olodaterol / Adrenergic Drugs _____ _____

Alert Message: Caution should be exercised when Striverdi Respimat (olodaterol) is prescribed concurrently with other adrenergic sympathomimetic agents, administered by any route, because the sympathetic effects of olodaterol may be potentiated.

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

Util A	Util B				Util C
Olodaterol	Ephedrine	Methyldopa	Phentermine	Naphazoline	
	Epinephrine	Tizanidine	Benzphetamine	Pirbuterol	
	Pseudoephedrine	Amphetamine	Diethylpropion	Metaproterenol	
	Phenylephrine	Dextroamphetamine	Phendimetrazine	Terbutaline	
	Clonidine	Lisdexamfetamine	Apraclonidine		
	Guanfacine	Methylphenidate	Brimonidine		

References:
Clinical Pharmacology, 2014 Gold Standard.
Striverdi Respimat Prescribing Information, July 2014, Boehringer Ingelheim Pharmaceuticals, Inc.

25. Olodaterol / Nonselective Beta-Blockers / Selective Beta-Blockers _____ _____

Alert Message: Concurrent use of a beta-adrenergic blocker with Striverdi Respimat (olodaterol) may diminish the pulmonary effect of the beta-agonist olodaterol. 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)**
Olodaterol	Carvedilol	Acebutolol
	Nadolol	Atenolol
	Labetalol	Betaxolol
	Penbutolol	Bisoprolol
	Pindolol	Metoprolol
	Propranolol	Nebivolol
	Sotalol	
	Timolol	

References:
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Striverdi Respimat Prescribing Information, July 2014, Boehringer Ingelheim Pharmaceuticals, Inc.

26. Olodaterol / Xanthines Derivatives, Steroids & K+ Depleting Diuretics _____ _____

Alert Message: Caution should be exercised when Striverdi Respimat (olodaterol) is prescribed concurrently with xanthine derivatives, steroids, or non-potassium sparing diuretics because concomitant administration may potentiate the hypokalemic effect of olodaterol. The ECG changes or hypokalemia that may result from the administration of non-potassium sparing diuretics can be acutely worsened by beta-agonists.

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

Util A	Util B			Util C
Olodaterol	Theophylline	Prednisolone	Chlorothiazide	
	Aminophylline	Prednisone	Chlorthalidone	
	Dyphylline	HCTZ		
	Betamethasone	Indapamide		
	Budesonide	Methyclothiazide		
	Cortisone	Metolazone		
	Dexamethasone	Furosemide		
	Hydrocortisone	Bumetanide		
	Methylprednisolone	Torsemide		

References:
Clinical Pharmacology, 2014 Gold Standard.
Striverdi Respimat Prescribing Information, July 2014, Boehringer Ingelheim Pharmaceuticals, Inc.

27. Olodaterol / Non-adherence _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Striverdi Respimat (olodaterol). 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: LR – Non-adherence
Drugs/Diseases

Util A	Util B	Util C
Olodaterol		

References:
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 COPD. 2010 Nov 24;5:401-406.

28. Dapagliflozin/Metformin / Overutilization _____ _____

Alert Message: The manufacturer's recommended maximum dose of Xigduo XR (dapagliflozin/metformin extended-release) is 10 mg/2000 mg per day.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Dapagliflozin/Metformin		

Max Dose: 10mg/200mgper day

References:
Xigduo XR Prescribing Information, Oct. 2014, AstraZeneca.

29 Dapagliflozin/Metformin / CKD Stage 3, 4 & 5 & ESRD _____ _____

Alert Message: Xigduo XR (dapagliflozin/metformin extended-release) use is contraindicated in patients with moderate to severe renal impairment (e.g., serum creatinine levels greater than or equal to1.5 mg/dL for men or 1.4 mg/dL for women, or eGFR < 60 mL/min/1.73 m^2 or CrCL < 60mL/min) and end-stage renal disease.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C**(Include)**
Dapagliflozin/Metformin		CKD Stage 3, 4 & 5 ESRD

References:
Xigduo XR Prescribing Information, Oct. 2014, AstraZeneca.

30. Dapagliflozin/Metformin / Therapeutic Appropriateness _____ _____

Alert Message: Assessment of renal function is recommended prior to initiation of Xigduo XR (dapagliflozin/metformin extended-release) therapy and verified as normal or no more than mildly impaired. Renal function should be assessed at least annually thereafter.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C**(Negate)**
Dapagliflozin/Metformin		CKD Stage 3, 4 & 5
		ESRD

References:
Xigduo XR Prescribing Information, Oct. 2014, AstraZeneca.

31. Dapagliflozin/Metformin / Insulin & Insulin Secretagogues _____ _____

Alert Message: The concurrent use of Xigduo XR (dapagliflozin/metformin extended-release) with insulin or an insulin secretagogue can increase the risk of hypoglycemia. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with dapagliflozin/metformin.

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

Util A	Util B	Util C
Dapagliflozin/Metformin	Insulin	
	Chlorpropamide	
	Tolbutamide	
	Tolazamide	
	Glyburide	
	Glipizide	
	Glimepiride	

References:
Xigduo XR Prescribing Information, Oct. 2014, AstraZeneca.

32. Dapagliflozin/Metformin / Hypotension _____ _____

Alert Message: The dapagliflozin component of Xigduo XR (dapagliflozin/metformin extended-release) can cause osmotic diuresis, which can lead to volume depletion and hypotension, particularly in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor patients for signs and symptoms during therapy. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected.

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

Util A	Util B	Util C
Dapagliflozin/Metformin	Hypotension	
	Hypovolemia	
	CKD Stage	
	Dehydration	

References:
Xigduo XR Prescribing Information, Oct. 2014, AstraZeneca.

33. Dapagliflozin/Metformin / Loop diuretics _____ _____

Alert Message: The dapagliflozin component of Xigduo XR (dapagliflozin/metformin extended-release) can cause osmotic diuresis, which can lead to volume depletion and hypotension, particularly in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor patients for signs and symptoms during therapy. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected.

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

Util A	Util B	Util C
Dapagliflozin/Metformin	Furosemide	
	Torsemide	
	Ethacrynate	
	Bumetanide	

References:
Xigduo XR Prescribing Information, Oct. 2014, AstraZeneca.

34. Dapagliflozin / Nonadherence _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Xigduo XR (dapagliflozin/metformin extended-release). Non-adherence 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
Dapagliflozin/Metformin		

References:
Xigduo XR Prescribing Information, Jan. 2014, Bristol-Myers Squibb.
Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med 2005;353:487-97.
Ho PM, Rumsfeld JS, Masoudi FA, et al., Effect of Medication Nonadherence in Diabetes Mellitus. Cardiology Review, April 2007.
Currie CJ, Peyrot M, Morgan CL, et al. The Impact of Treatment Noncompliance on Mortality in People With Type 2 Diabetes. Diabetes Care 35:1279-1284, June 2012.

35. Dapagliflozin/Metformin / LDL-C Increases _____ _____

Alert Message: The use of Xigduo XR (dapagliflozin/metformin extended-release) can cause dose-related increases in LDL-C levels due to the dapagliflozin component. Patients receiving dapagliflozin/metformin should have their LDL-C levels monitored and treated per standard of care.

Conflict Code: TA – Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Dapagliflozin/Metformin		Hypercholesterolemia

References:
Xigduo XR Prescribing Information, Oct. 2014, AstraZeneca.

36. Dapagliflozin/Metformin / Bladder Cancer _____ _____

Alert Message: In clinical trials, an increased occurrence of bladder cancer was observed in subjects receiving dapagliflozin (0.17%) as compared to placebo (0.03%). Xigduo XR (dapagliflozin/metformin extended-release) should not be used in patients with active bladder cancer and used with caution in patients with a prior history of bladder cancer.

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

Util A	Util B	Util C **(Include)**
Dapagliflozin/Metformin		Neoplasm of Bladder
		History of Malignant Neoplasm of Bladder

References:
Xigduo XR Prescribing Information, Oct. 2014, AstraZeneca.

37. Vorapaxar / Overutilization _____ _____

Alert Message: The manufacturer's recommended dose of Zontivity (vorapaxar) is one 2.08 mg tablet once daily.

Conflict Code: ER - Overutilization
Drugs/Diseases

Util A	Util B	Util C
Vorapaxar		

Max Dose: 2.08 mg /day

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

38. Vorapaxar / Therapeutic Appropriateness (Black Box Warning) _____ _____

Alert Message: Zontivity (vorapaxar) use is contraindicated in patients with a history of stroke, transient ischemic attack (TIA), intracranial hemorrhage (ICH), or active pathological bleeding. Vorapaxar is an antiplatelet agent which increases the risk of bleeding including ICH and fatal bleeding. Discontinue vorapaxar in patients who experience a stroke, TIA, or ICH.
Conflict Code: TA – Therapeutic Appropriateness (Black Box – Contraindication)
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Vorapaxar		Stroke
		Transient Ischemic Attack
		Intracranial Hemorrhage
		Peptic Ulcer Bleeding

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

39. Vorapaxar / Other Antiplatelet Agents Negating _____ _____

Alert Message: A review of recent pharmacy claims for the patient does not show the use of Zontivity (vorapazar) with aspirin and/or clopidogrel according to their indications and standard of care. There is no experience with the use of vorapaxar alone as the only administered antiplatelet agent.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Negating)**
Vorapaxar		Aspirin
		Clopidogrel

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

40. Vorapaxar / Other Antiplatelet Agents Negating _____ _____

Alert Message: The concurrent use of Zontivity (vorapaxar) with other antiplatelet drugs may result in a potential additive effect for bleeding. Vorapaxar is indicated for combination therapy with aspirin and/or clopidogrel, but there is limited clinical experience with the use of vorapaxar with other antiplatelet drugs.

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

Util A	Util B	Util C
Vorapaxar	Dipyridamole	
	Ticlopidine	
	Cilostazol	
	Prasugrel	
	Ticagrelor	
	Anagrelide	

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

41. Vorapaxar / Anticoagulants _____ _____

Alert Message: The concurrent use of Zontivity (vorapaxar) with warfarin or other anticoagulants should be avoided. Vorapaxar is a platelet aggregation inhibitor and concomitant use with an anticoagulant may have an additive effect, increasing the risk of bleeding.

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

Util A	Util B	Util C
Vorapaxar	Warfarin	
	Dabigatran	
	Apixaban	
	Rivaroxaban	
	Enoxaparin	

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

42. Vorapaxar / Agents Affecting Hemostasis _____ _____

Alert Message: Caution should be exercised when Zontivity (vorapaxar) is prescribed with drugs that affect hemostasis (e.g., chronic NSAIDS, SSRIs, and SNRIs) as concomitant use of these agents may increase the risk of bleeding. Patients should be instructed to monitor for signs and symptoms of bleeding during concurrent use and promptly report any bleeding events.

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

Util A	Util B	Util C
Vorapaxar	NSAIDS	
	SSRIs	
	SNRI's	

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

43. Vorapaxar / Strong CYP3A4 Inhibitors _____ _____

Alert Message: Concurrent use of Zontivity (vorapaxar) with strong CYP3A4 inhibitors should be avoided. Vorapaxar is a CYP3A4 substrate and use with a strong inhibitor of CYP3A4-mediated metabolism may result in increased vorapaxar exposure and risk of bleeding.

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

Util A	Util B		Util C
Vorapaxar	Nefazodone	Ketoconazole	
	Clarithromycin	Itraconazole	
	Telithromycin	Posaconazole	
	Saquinavir	Voriconazole	
	Ritonavir	Boceprevir	
	Indinavir	Telaprevir	
	Nelfinavir		

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

44. Vorapaxar / Strong CYP3A4 Inducers _____ _____

Alert Message: Concurrent use of Zontivity (vorapaxar) with strong CYP3A4 inducers should be avoided. Vorapaxar is a CYP3A4 substrate and use with a strong inducer of CYP3A4-mediated metabolism may result in decreased vorapaxar exposure and loss of efficacy.

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

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

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

45. Vorapaxar / Hepatic Impairment _____ _____

Alert Message: Based on the inherent risk of bleeding in patients with severe hepatic impairment, Zontivity (vorapaxar) is not recommended in such patients. No dosage adjustment is required in patients with mild and moderate hepatic impairment.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C **(Include)**
Vorapaxar		Hepatic Impairment

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.

46. Vorapaxar / Non-adherence _____ _____

Alert Message: Based on refill history, your patient may be under-utilizing Zontivity (vorapaxar). Non-adherence 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
Vorapaxar		

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Osterberg L, Blaschke T. Adherence to Medication. N Engl J Med 2005; 353:487- 497.
Kumbhani DJ, Steg PG, Cannon CP, et al. Adherence to Secondary Prevention Medications and Four-year Outcomes in Outpatients With Atherosclerosis. Am J Med. 2013 Aug;126(8):693-700. http://dx.doi.org/10.1016/j.amjmed.2013.01.033.
Kneeland PP, Fang MC. Current Issues in Patient Adherence and Persistence: Focus on Anticoagulants for the Treatment and Prevention of Thromboembolism. Pat Pref Adher 2010;4:51-60.
Ferguson C, Inglis SC, Newton PJ, et al. Atrial Fibrillation and Thromboprophylaxis in Heart Failure: The Need for Patient-centered Approaches to Address Adherence. Vascular Health and Risk Management 2013;9:3-11.

47. Vorapaxar / Therapeutic Appropriateness _____ _____

Alert Message: The safety and effectiveness of Zontivity (vorapaxar) in pediatric patients have not been established.

Conflict Code: TA - Therapeutic Appropriateness
Drugs/Diseases

Util A	Util B	Util C
Vorapaxar		

Age Range: 0-18 yoa

References:
Zontivity Prescribing Information, May 2014, Merck Sharp & Dohme Corp.
Clinical Pharmacology, 2014 Elsevier/Gold Standard.
Facts & Comparisons, 2014 Updates, Wolters Kluwer Health.