HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on October 15, 2021 via MS Teams. The meeting was called to order by Dr. Moron, Chair at 9:31 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Yekini Adeyemi, RN	Absent	David Moron, MD- Chair	Present
Angela Babin, RPh	Present	Leah Nunez, PharmD	Present
Jean Baemayr, PharmD- Secretary	Present	Brittany Parmentier, PharmD	Present
John Bennett, MD	Present	Kenda Pittman, PharmD	Absent
Giovanna Betancourt, PharmD	Present	Rishi Sawhney, MD	Absent
Rakesh Chadalavada, MD	Present	Charlene Shero, MD	Present
German Corso, MD	Present	Glenn Shipley, DO	Present
Brad Fitzwater, MD	Present	Lesia Trickett, MD	Present
Catherine Hall, PharmD	Present	Ashton Wickramasinghe, MD	Present
Dana Hopkins, RN	Present	Patrick Young, MD	Present
Jeffery Matthews, MD	Absent		

Guests Present: Tonya Barrios, State Hospitals Central Administration; Allison Tiemann, P4 PharmD Student, UT Health East Texas; Rania Kattura, PharmD, Austin State Hospital; Oswaldo Ramirez, PharmD, El Paso Psychiatric Center; Ashlynn Zeiger, P4 PharmD Student, UT El Paso School of Pharmacy

Opening

Introduction and Other Information

Dr. Charlene Shero, North Texas State Hospital, Wichita Falls, has been selected as a state hospital physician member of the committee.

Conflict of Interest Disclosures

The committee members present did not disclose any new conflicts of interest.

Review of Minutes

The minutes from the July 9, 2021 meeting were approved as previously distributed.

Unfinished Business

Reserve Use Criteria – methadone (April 2021)

New Business

Prescription Digital Therapeutics

The committee briefly discussed whether prescription digital therapeutics fell under the purview of the PEFC. Dr. Fitzwater will check with Texas HHSC Medicaid services to see how they handle these products.

Adverse Drug Reaction Reports

The committee discussed one adverse drug reaction report that was received from the field. This adverse event was reported to the FDA's MedWatch program.

ADR: clozapine/ altered mental status, shortness of breath (SOB), dizziness, falls, orthostasis, dehydration, constipation
A 52-year-old edentulous Hispanic female with diagnoses of schizoaffective disorder, seizure disorder, hypertension, diabetes, hypothyroidism, history of alcohol abuse, and constipation was transferred from a state hospital to a medical hospital on 5/19/21 due to unresponsiveness, minimal voluntary movement of extremities, and pinpoint pupils. Her skin appeared jaundiced, but not her eyes. Blood pressure (BP) and pulse were within normal limits (WNL). Labs 5/18/21: glucose = 275 mg/dL, albumin = 2.6 g/L (3.4-4.7), alkaline phosphatase (ALP) = 261 units/L (38-126), ammonia = 38 ug/dL (15-45). Medications were clozapine 250 mg daily at bedtime; valproic acid 1000 mg and 1500 mg; levetiracetam 1000 mg twice daily; levothyroxine 175 mcg once daily; pantoprazole 40 mg once daily; benztropine 0.5 mg twice daily; sliding scale insulin; fludrocortisone 0.2 mg once daily in the morning; midodrine 10 mg three times daily; bisacodyl 5 mg; lactulose 30 ml twice daily; Miralax 17 grams twice daily. She was non-compliant with laxatives. On 5/19/21, clozapine = 1322 ng/mL, norclozapine = 361 ng/mL on clozapine 250 mg daily.
The patient had been hospitalized several times in the preceding 6 months:
Late December 2020: Sent out for fluids after falling and appearing unresponsive. Medications: clozapine 600 mg per day, chlorpromazine 500 mg per day, Depakote DR 1000 mg twice daily; benztropine 0.5 mg twice daily; levetiracetam 1000 mg twice daily; levothyroxine; insulin glargine, metformin 1000 mg twice daily, empagliflozin 25 mg once daily. No clozapine level available. Covid-19 positive with symptoms, she received bamlanivimab infusion at the state hospital when she returned from community hospital. Around this time, she was started on fludrocortisone for orthostatic hypotension from clozapine and chlorpromazine.
1/19/21-1/24/21: Dizziness, confusion, altered gait, slow responses, staring. Doctors at the community hospital diagnosed pneumonia but the state hospital physician

didn't agree with the diagnosis. Medications: clozapine 600 mg per day, chlorpromazine 500 mg per day, pantoprazole plus the other meds listed above. On 1/29/21, clozapine = 1170 ng/mL, norclozapine = 299 ng/mL on clozapine 600 mg daily.
4/28/21-5/4/21: Vomiting, constipation, dizziness, orthostasis. She had lost 40 pounds since December 2020; she attributed the weight loss to her dislike for her ground diet which was started in February 2021 because of choking episodes. Labs 4/28/21: aminotransferase alanine (ALT) = 175 units/L (10-60), aminotransferase aspartate (AST) = 159 units/L (10-42), ALP = 203 units/L (38-126). Lipase < 4 (WNL). ALT/AST, ALP had been normal in January 2021. On 4/28/21, the state hospital psychiatrist discontinued chlorpromazine 100 mg three times daily because of dizziness, low BP, and its possible contribution to cholestatic hepatitis. The patient was taking clozapine 400 mg daily plus the other meds listed above. On 4/27/21, clozapine > 1500 ng/mL, norclozapine = 333 ng/mL on clozapine 400 mg daily. During hospitalization, an abdominal CT scan showed fatty liver, constipation, ground-glass opacities suggesting viral illness, and fatty replacement of pancreas with calcifications. An echocardiogram was normal (performed because of the possibility of Covid-19 complications causing orthostasis). Brain CT scan was normal. Upon return to the state hospital on 5/4/21, she was still feeling light-headed and her psychiatrist lowered clozapine to 300 mg once daily at bedtime. On 5/10/21, clozapine = 2176 ng/mL, norclozapine = 418 ng/mL on clozapine 300 mg daily.

The above hospitalizations were secondary to a combination of the following factors: altered mental status (confusion, unresponsiveness, slow responses, staring), SOB)(especially in December-January when she had an acute Covid-19 infection), dizziness, falls, orthostasis, dehydration, constipation. Other than SOB and dehydration, the combination of high clozapine levels and chlorpromazine (discontinued 4/28/21) could have been contributing to all of these. The patient's clozapine levels remained elevated despite dose reductions.

1/29/21: clozapine = 1170 ng/mL (60-1000 ng/ml), norclozapine = 299 ng/mL (50-1500 ng/ml) on clozapine 600 mg daily
4/27/21: clozapine > 1500 ng/mL, norclozapine = 333 ng/mL on clozapine 400 mg daily
5/10/21: clozapine = 2176 ng/mL, norclozapine = 418 ng/mL on clozapine 300 mg daily
5/19/21: clozapine = 1322 ng/mL, norclozapine = 361 ng/mL on clozapine 250 mg daily
All clozapine:norclozapine ratios were > 3 which suggests metabolic inhibition or a non-trough level. Lexicomp did not list any pharmacokinetic interactions with her medication list, clozapine levels were drawn at the appropriate times, and MAR revealed that correct doses had been administered. We speculated that lingering Covid-19 infection was contributing to elevated clozapine levels. CYP1A2 is responsible for approximately 70% of clozapine's metabolism; increases in

inflammatory mediators have been associated with reduced CYP1A2 expression resulting in decreased clozapine metabolism and an increased clozapine:norclozapine ratio.

New Drug Applications

Conflict of Interest disclosure forms were previously received from the non-committee members who had submitted the new drug application and/or prepared the monograph. No new conflicts were disclosed.

Ezetimibe (Zetia)

Presented by Allison Tiemann, P4 PharmD Student. Please refer to Appendix A for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of ezetimibe to the formulary in the Antihyperlipidemic Agents section.

The formulary check list was completed and no issues were detected.

Deutetrabenazine (Austedo)

Pended until the January committee meeting.

HHSC Psychiatric Drug Formulary Tables Annual Review

The committee reviewed and approved recommended revisions to the following tables:

- Psychotropic dosage guidelines
- Reserve Drugs
- Therapeutic Serum Concentrations

The updated formulary will be posted to the PEFC website.

Other Formulary Changes

The committee reviewed and approved changes that remove redundancy in the passages referring to reserve drugs ("Introduction", "Procedure for Addition of Drugs to the Formulary", "Reserve Drugs.")

Psychotropic Medication Guidelines- recommended changes to metabolic syndrome monitoring

The State Hospital Medical Executive Committee had asked that the PEFC review the psychotropic monitoring guidelines and consider changing waist circumference to an optional monitoring parameter, due to the difficulty in consistently obtaining accurate measurements of abdominal girth. Dr. Kattura presented a review of the three most commonly used guidelines for determining a diagnosis of metabolic syndrome. Upon review of the literature and with understanding of the comorbidities that patients

within the state hospitals and state supported living center face, the committee recommended to keep the psychotropic audit criteria unchanged to ensure a more accurate assessment of cardiovascular risk.

Changes to the Clozapine REMS Program

The committee discussed the upcoming modifications to clozapine REMS. Of note:

- Prescribers and pharmacies must be re-certified in the new system by November 15, 2021 or they will no longer be able to prescribe/dispense clozapine.
- Prescribers must re-enroll their current patients by November 15, 2021. Patients who are not re-enrolled by that day will no longer be able to receive clozapine.
- Pharmacists cannot enroll as designees for multiple providers using the same email address. Most pharmacists in our system are currently acting as designees for several providers.
- The state hospital pharmacies are enrolling as in-patient pharmacies. This allows the pharmacist to search for patients and update labs, but they cannot update patient profiles or enroll patients. Pharmacists can use paper forms to enroll patients, change enrollment status, and change providers. This form does not require them to sign as a designee.

Quarterly Non-Formulary Drug Justification Report

For the fourth quarter of fiscal year 2021 (June 2021 through August 2021), only the state hospitals reported use of non-formulary agents. The state supported living centers (SSLCs) currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top five non-formulary agents, by number of orders, that were prescribed in the state hospitals during the fourth quarter of fiscal year 2021:

- Modafinil
- Magnesium oxide
- Promethazine HCL injection
- Acetaminophen/caffeine/pyrilamine (Midol Menstrual Complete)
- Listerine Zero

Drug Formulary Sectional Review

In reviewing the formulary drug listings for infectious disease and antineoplastic agents, the following changes were approved:

- Antibiotics-Tetracyclines Agents
  - Minocycline- remove capsule, pellet filled, oral (leaving capsule, oral)
- Antibiotics-Quinolones Agents
  - Moxifloxacin- remove Infusion

- Antituberculars Agents
  - Isoniazid (INH)- remove Injection
  - Rifampin-Isoniazid (Rifamate) capsules- remove; product is obsolete
- Updated Cost Index of several items

The updated formulary will be posted on the PEFC website.

HHSC Psychiatric Drug Formulary Annual Review

The committee reviewed and approved the 2022 HHSC Psychiatric Drug Formulary.

Issues from the Chief Medical Officer, State Hospitals

Dr. Matthews was not present to present a report.

Issues from the Medical Services Coordinator, SSLCs

Dr. Shipley reported the SSLCs have used REGEN-COV (casirivimab and imdevimab) on a few patients who are unvaccinated or immunocompromised for prophylaxis treatment. The SSLCs have also started giving the Pfizer booster to patients and staff and are awaiting FDA approval for the Moderna and Johnson and Johnson booster.

Drug Shortages, Recalls, and FDA Safety Communications

The FDA has issued the following safety communications and recalls that may impact our facilities:

Recalls

Chantix (varenicline)**:** Pfizer is recalling all lots of Chantix tablets due to the presence of a nitrosamine, N-nitroso-varenicline, above the Pfizer established Acceptable Daily Intake (ADI) level. Long-term ingestion of N-nitroso-varenicline may be associated with a theoretical potential increased cancer risk in humans, but there is no immediate risk to patients taking this medication. The health benefits of stopping smoking outweigh the theoretical potential cancer risk from the nitrosamine impurity in varenicline. To date, Pfizer has not received any reports of adverse events that have been related to this recall.

Glucagon emergency kit: Eli Lilly and Company is recalling lot D239382D, Expiration April 2022, of Glucagon Emergency Kit for Low Blood Sugar (glucagon for injection, 1 mg per vial; diluent for glucagon, 1 mL syringe) because of a product complaint reporting that the vial of glucagon was in liquid form instead of the powder form. The firm's investigation indicates that the liquid in this glucagon vial could be related to the manufacturing process. The use of the liquid form of this product may fail to treat severe low blood sugar due to loss of potency.

Lotrimin AF and Tinactin spray: Bayer is recalling all unexpired Lotrimin AF and Tinactin spray products with lot numbers beginning with TN, CV or NAA, distributed between September 2018 to September 2021, due to the presence of benzene in

some samples of the products. Benzene is classified as a human carcinogen. Exposure to benzene can occur by inhalation, orally, and through the skin. Depending on duration and level of exposure, it can result in cancers including leukemia, and blood cancer of the bone marrow and blood disorders which can be life-threatening. Benzene is found in the environment from natural sources and human activity. Humans around the world are exposed to it from multiple sources and pathways, including inhalation, through the skin, and orally. To date, Bayer has no known reports of adverse events related to this recall.

Safety-related Labeling Changes

Vyvanse (lisdexamfetamine dimesylate): Additions underlined

Warnings and Precautions/ Suppression of Growth: Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. Vyvanse is not approved for use in pediatric patients below 6 years of age.

Pediatric Use: Safety and efficacy of Vyvanse were evaluated in a double-blind, randomized, parallel-group, placebo-controlled, fixed-dose study in pediatric patients ages 4 to 5 years with ADHD, followed by a 1-year open-label extension study. In these studies, patients experienced elevated rates of adverse reactions, including weight loss, decreased BMI, decreased appetite, insomnia, infections (upper respiratory and nasopharyngitis), irritability, and affect lability. With the same Vyvanse dose, mean steady state exposure of dextroamphetamine was approximately 44% higher in pediatric patients ages 4 to 5 years compared to the pediatric patients ages 6 to 11 years.

Ultram (tramadol hydrochloride): Newly added subsections

Hyponatremia: Hyponatremia (serum sodium < 135 mmol/L) has been reported with the use of tramadol, and many cases are severe (sodium level < 120 mmol/L). Most cases of hyponatremia occurred in females over the age of 65 and within the first week of therapy. In some reports, hyponatremia resulted from the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Monitor for signs and symptoms of hyponatremia (e.g., confusion, disorientation), during treatment, especially during initiation of therapy. If signs and symptoms of hyponatremia are present, initiate appropriate treatment (e.g., fluid restriction) and discontinue tramadol.

Hypoglycemia: Cases of tramadol-associated hypoglycemia have been reported, some resulting in hospitalization. In most cases, patients had predisposing risk factors (e.g. diabetes). If hypoglycemia is suspected, monitor blood glucose levels and consider drug discontinuation as appropriate.

SSRIs, SNRIs: Newly added subsection

Sexual Dysfunction: Use of SSRIs and SNRIs may cause symptoms of sexual dysfunction. In male patients, SNRI use may result in ejaculatory delay or failure,

decreased libido, and erectile dysfunction. In female patients, SNRI use may result in decreased libido and delayed or absent orgasm. It is important for prescribers to inquire about sexual function prior to initiation and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

News Briefs

The following information was shared with the committee members:

Gilead Seeking FDA Approval For Investigational Long-Acting HIV Treatment
Healio (7/6, Downey) reports, "Gilead Sciences submitted a new drug application to the FDA for the approval of lenacapavir, an investigational, long-acting HIV-1 capsid inhibitor that is given subcutaneously every 6 months." Key six-month data for the drug "will be presented during the International AIDS Society (IAS) Conference this month, Gilead said."

GSK, Shionogi To Develop Longer-Acting HIV Treatment
Reuters (9/28, Aripaka) reports GlaxoSmithKline "said on Tuesday it would develop an HIV treatment with Japan's Shionogi for use in regimens with dosing gaps of three months or more."

Shionogi Launches Human Trials For Once Daily Tablet For Treating COVID
The Wall Street Journal (7/25, Landers, Subscription Publication) reports Japanese drugmaker Shionogi has launched human trials of the first once-a-day tablet for patients with COVID-19. The Japanese company is months behind Pfizer and Merck & Co., which have therapies for treating COVID-19 in later-stage tests. The Pfizer and Shionogi tablets block infections by inhibiting proteases, the Wall Street Journal reported.

FDA Approves Twice-Yearly Injectable Schizophrenia Treatment
HCPlive (9/1) reports, "The US Food and Drug Administration (FDA) has approved a 6-month paliperidone palmitate (INVEGA HAFYERA), a long-acting atypical antipsychotic for the treatment of adult patients with schizophrenia," a press release announced. The treatment is "the first-and-only twice-yearly injectable treatment for schizophrenia."

FDA Grants Priority Review For Intranasal Prader-Willi Syndrome Treatment
Healio (7/9) reported, "The FDA granted priority review for a new drug application for an intranasal oxytocin analogue to reduce hyperphagia and behavioral distress associated with Prader-Willi syndrome, according to" a press release on the Foundation for Prader-Willi Research's website. The agency's "six-month priority review will accelerate the review process and a decision from the FDA regarding the

approval of LV-101 (intranasal carbetocin, Levo Therapeutics) should be made by the end of the year, according to the release."

FDA Approves Shingrix Vaccine For Use In Adults 18 Years And Older With Increased Risk Of Immunodeficiency Or Immunosuppression
HCPlive (7/26, Butera) reports in a July 26 news release, GlaxoSmithKline announced the FDA's approval of "the non-live, recombinant sub-unit adjuvanted vaccine Shingrix for the prevention of shingles in adults aged 18 years and older with increased risk of immunodeficiency or immunosuppression." In 2017, the agency approved the vaccine "for the prevention of shingles in adults 50 years or older."

Eisai Pursuing Approval Of Alzheimer's Drug Through Accelerated Approval
Reuters (9/27, Steenhuysen) reports, "Japanese drugmaker Eisai Co on Monday began its application process for its experimental drug for early Alzheimer's disease using an accelerated approval pathway." The company, "which leads development on Alzheimer's drug lecanemab, is using evidence from a midstage trial showing its drug candidate removes brain plaques to an even greater degree than Aduhelm, with lower rates of brain swelling." Eisai also "already has a confirmatory, Phase III trial fully enrolled."

Open Forum

October 17-23 is National Pharmacy Week, which "acknowledges the invaluable contributions pharmacists and technicians make to patient care in hospitals, outpatient clinics, and other healthcare settings."

Next Meeting Date

The next meeting is scheduled for January 28, 2022.

Adjourn

There being no further business, the meeting was adjourned at 1:48 p.m.

Approved: *David Moron*

David Moron, MD, Chairman

Minutes Prepared by:
Tonya Barrios, PhTR
Reviewed by:
Jean Baemayr, PharmD

Appendix A

Ezetimibe (Zetia™)

Classification

Antihyperlipidemic agent

Pharmacology

Ezetimibe inhibits the absorption of cholesterol in the small intestine. The drug's target is a specific sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), located at the brush border of the small intestine. Ezetimibe binds to the transporter to prevent the intestine from absorbing cholesterol and phytosterols into the blood and their subsequent transportation to the liver. The overall effect results in a decrease in cholesterol storage within the liver and an increase in cholesterol clearance from the blood.

Indication

Ezetimibe is indicated alone or in combination with a HMG-CoA reductase inhibitor (statin) in primary hyperlipidemia, in combination with fenofibrate in mixed hyperlipidemia, in combination with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia, and in patients with homozygous sitosterolemia (phytosterolemia). For all indications, ezetimibe is indicated as adjunctive therapy to diet.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Upon oral administration, ezetimibe is absorbed and conjugated into an active phenolic glucuronide (ezetimibe-glucuronide). Time to reach ezetimibe peak plasma concentration is 4 to 12 hours and time to reach the glucuronide conjugate peak plasma concentration is 1-2 hours. Consumption of ezetimibe 10mg tablet with food showed no significant alterations in absorption. Consuming high fat meals resulted in a 38% increase in Cmax.
Distribution	Ezetimibe and ezetimibe-glucuronide are highly plasma protein bound (>90%).
Metabolism	Ezetimibe undergoes rapid glucuronide conjugation (a phase II reaction) to an active metabolite in the liver and small intestine. Oxidative metabolism (a phase I reaction) of ezetimibe occurs minimally. Both ezetimibe and the conjugate have a half-life of 22 hours. The conjugate is the most common form found in the plasma. Enterohepatic recycling is likely considering the variations in plasma concentration time levels.

Pharmacokinetic Parameter	Details
Excretion	Ezetimibe undergoes elimination primarily through the biliary tract and kidneys. Upon oral administration of ezetimibe 20 mg, 78% of the administered dose was detected in the stool and 11% in the urine.

Dosage/Administration

- Recommended dose is 10mg daily with or without food.
- Ezetimibe can be taken at the same time as a statin or fenofibrate.
- Ezetimibe should be administered ≥2 hours before or ≥4 hours after bile acid sequestrants.

Use in Special Populations

Pregnancy: There is a lack of quality data in pregnant women. Animal studies have found that ezetimibe crosses the placenta and in rats doses ~10x the human exposure resulted in increased incidences of common fetal skeletal findings. Ezetimibe should only be used in pregnancy if the benefits outweigh the risks.

Lactation: It is unknown if ezetimibe is excreted into human breast milk. It should only be used in nursing mothers if the benefits outweigh the risks.

Pediatric Use: Ezetimibe has been studied in combination with simvastatin in adolescent boys and girls 10 to 17 years of age with heterozygous familial hypercholesterolemia. The dose for ezetimibe in pediatrics is 10 mg once daily. There were no significant effects on growth or sexual maturation in adolescent boys or girls in the studies. There are no pharmacokinetic differences of ezetimibe between adolescents and adults.

Geriatric Use: No dosage adjustments necessary.

Hepatic Impairment: No dosage adjustment necessary in mild hepatic impairment.

Renal Impairment: No dosage adjustment necessary in renal impairment.

Contraindication

- Pregnancy or woman who may become pregnant
- Breastfeeding
- Known hypersensitivity to any component of the product
- Ezetimibe in combination with a stain is contraindicated in acute liver disease or unexplained persistent elevations in hepatic transaminase levels

Precautions

- Consider discontinuing ezetimibe and/or statin if AST or ALT elevations persist above 3x upper normal limit.

- Ezetimibe with or without a statin may result in myopathy and rhabdomyolysis. If this is suspected or confirmed, ezetimibe and any statin or fibrate should be discontinued immediately.
- Ezetimibe is not recommended in patients with moderate to severe hepatic impairment.

Adverse Effects

In studies of ezetimibe monotherapy, the adverse reactions that occurred in 2% or more of patients and had a higher incidence than placebo included: diarrhea (4.1%), fatigue (2.4%), influenza (2%), sinusitis (2.8%), upper respiratory tract infection (4.3%), arthralgia (3%), and extremity pain (2.7%).

Adverse reactions in studies of ezetimibe with a statin compared to statin monotherapy were similar.

Monitoring

Toxicity: LFTs at baseline; if used in combination with a statin, LFTs when clinically indicated; if used in combination with fenofibrate, monitor LFTs when clinically indicated and signs and symptoms of cholelithiasis

Efficacy: Total cholesterol, HDL, LDL, triglycerides at baseline, 4-12 weeks after starting, then every 3-12 months

Interactions

Agent	Interaction	Management
Cyclosporine	Increased exposure to ezetimibe and cyclosporine	Monitor cyclosporine concentrations Consider risks/benefits of increased ezetimibe exposure
Cholestyramine	Decreased ezetimibe absorption	Take ezetimibe 2 hours before or 4 hours after cholestyramine
Fibrates (ezetimibe has only been studied with fenofibrate)	Increased risk of cholelithiasis	Avoid concurrent use or monitor closely for cholelithiasis
Warfarin	Increased bleeding risk	Monitor INR and adjust dosage accordingly

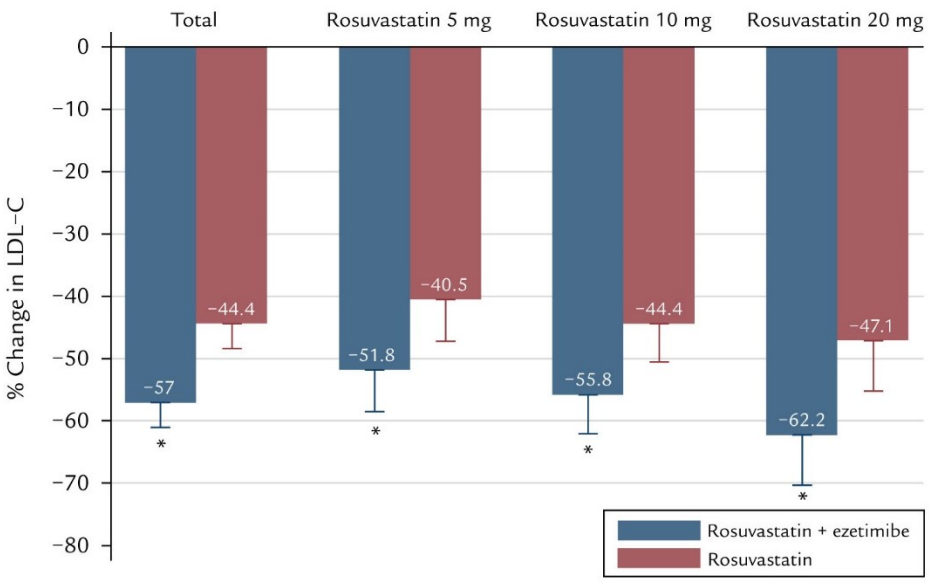
Efficacy

Studies have shown efficacy for ezetimibe in LDL reduction when used alongside statins. The IMPROVE-IT trial, published in 2015, analyzed the effect of simvastatin 40 mg + ezetimibe 10 mg compared to simvastatin 40 mg + placebo in over 18,000

patients. Patients were eligible for inclusion if they were ≥50 years of age, had an acute coronary syndrome within the previous 10 days, and had LDL >50 mg/dL. Patients had a follow up visit at 1 month, 4 months, and then every 4 months afterwards. The primary efficacy end point was a composite of death from cardiovascular disease, a major coronary event, or nonfatal stroke. Prespecified goals for LDL-C were < 70 mg/dL and for high sensitivity C-reactive protein (hs-CRP) were < 2 mg/L at 1 month. 50.6% of patients in the ezetimibe/simvastatin group met both of these outcomes compared to 30.5% in the simvastatin group ($p<0.001$). The combination of ezetimibe/simvastatin provided 24% further reduction of LDL cholesterol when compared to simvastatin alone. At 1 year, total cholesterol, triglycerides, non-HDL-C, apolipoprotein B, and hs-CRP were also significantly lower in the combination group compared to the simvastatin monotherapy group. Event rates for the primary efficacy end points were 32.7% in the combination group compared to 34.7% in the monotherapy group ($p=0.016$). There were no significant differences in side effects among the two groups.

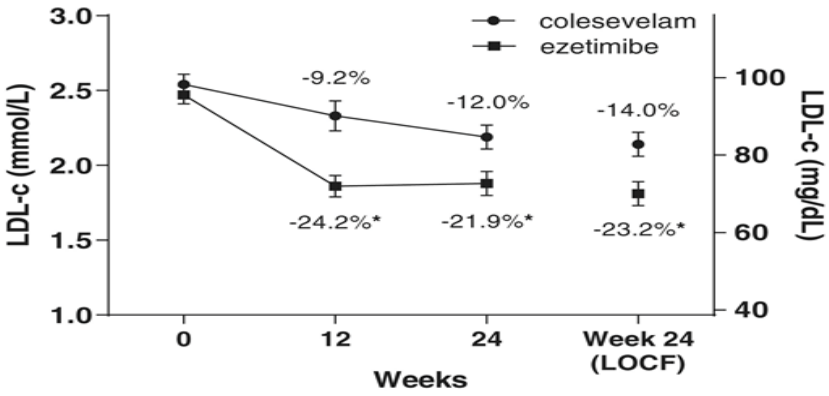
In another efficacy study (I-ROSETTE), ezetimibe + rosuvastatin was compared to rosuvastatin alone in those with hypercholesterolemia. In this 8 week phase III, multicenter, double-blind, randomized controlled trial, participants were randomized to receive either ezetimibe 10mg/rosuvastatin 20mg, ezetimibe 10mg/rosuvastatin 10mg, ezetimibe 10mg/rosuvastatin 5mg, rosuvastatin 20mg, 10mg, or 5mg.

The primary end point was the mean percent change in LDL-C levels from baseline to 8 weeks between the combination ezetimibe/rosuvastatin group compared to the monotherapy rosuvastatin group. 396 subjects completed the study and 389 were analyzed. Results showed that the percent changes in LDL-C from baseline to week 8 were -57.0% and -44.4% in the total combination and total rosuvastatin groups, respectively. The number of participants who reached target LDL-C levels according to the NCEP ATP III guidelines were significantly greater in the total ezetimibe/rosuvastatin group (180 [92.3%]) than in the rosuvastatin monotherapy arm (155 [79.9%]) ($p<0.001$). The two most common adverse effects (AEs) were infections in the rosuvastatin 5mg arm at 6.2% and gastrointestinal disorders in the ezetimibe 10mg/rosuvastatin 20mg group at 6.1%. No significant differences were found in reported AEs and adverse drug reactions between the four treatment groups. All safety parameters collected and analyzed were determined to be similar among the treatment arms.



Hong SJ et al. Clin Therapeutics 2018; 40:226-241.

More recent studies have continued to evaluate ezetimibe's use particularly in those with type II diabetes already on statin therapy. A study was performed to determine the efficacy and safety of colesevelam and ezetimibe in lowering LDL-C levels in those with type II diabetes. The trial was a 24-week, multicenter, open label, 1:1, randomized, pragmatic clinical study with two treatment arms colesevelam 3.75g once or twice daily with a meal and ezetimibe 10mg once at the same time every day with or without a meal. Subjects enrolled were required to have a diagnosis of T2D for >6 months, HbA1c of 7.1% to 10%, LDL >2.0mmol/L (77.34mg/dL), and stable diabetes medications and a statin medication for at least three months. Laboratory monitoring occurred at baseline, 12 weeks, and 24 weeks and included HbA1c, LDL-C, fasting plasma glucose (FPG), high density lipoprotein-cholesterol (HDL-C), non-HDL-c, triglycerides, ALT, CK, and CRP. 186 subjects were randomized and received a dose of study medication with 89 participants in the colesevelam group and 97 participants in the ezetimibe group. The primary endpoint was the proportion of patients who achieved the goal levels for both LDL-C (≤2.0mmol/L [77.34mg/dL]) and HbA1c (≤7.0%) at 24 weeks. The proportion of patients in the colesevelam group that achieved both goals was 14.6% compared to 10.5% in the ezetimibe group. These results show that colesevelam was non-inferior to ezetimibe but it was not superior to ezetimibe. Additionally, significant reductions in LDL-C from baseline to 24 weeks were found in both treatment groups (14% for colesevelam and 23.2% for ezetimibe) with the ezetimibe arm showing a significantly greater reduction (p=0.01). Adverse events were significantly higher with colesevelam compared to ezetimibe (20.2% vs. 7.2%, p=0.009). Study drug discontinuation also occurred more frequently in the colesevelam group compared to ezetimibe (31.1% vs. 6.2%,



Week	0 (baseline)	12	24	24 (LOCF)
colesevelam (n)	82	77	77	82
ezetimibe (n)	94	92	89	94

Bajaj HS et al. Diabetes Obes Metab 2020; 22:1722-1728.

p=<0.001).

Conclusions from Literature:

For individuals with primary hypercholesterolemia and mixed hyperlipidemia, ezetimibe 10mg in combination with a statin has shown greater lipid lowering benefits in clinical trials than statin monotherapy. In certain instances, such as documented intolerance to the lowest doses of hydrophilic statins (atorvastatin and rosuvastatin) ezetimibe may be used as monotherapy to lower lipid levels. In patients who have atherosclerotic cardiovascular disease and whose LDL-C remains ≥1.8mmol/L (≥70mg/dL) after maximally tolerated statin therapy the AHA/ACC 2018 guidelines recommend initiation of ezetimibe. Compared to statins, the most common adverse effects of ezetimibe have involved gastrointestinal discomfort and elevated hepatic enzymes but neither have shown to cause significant distress or impairment.

Dosage Forms/Cost[6]

Name	Form	Strength	AWP/tablet	30 day supply (AWP)
Ezetimibe	Tablet	10 mg	~$11	$330

Special Considerations

None

Summary/Conclusion

Ezetimibe is FDA approved as monotherapy or as combination therapy for a variety of lipid abnormalities. In all indications, it is to be given as an adjunctive therapy to diet modifications. Ezetimibe has a favorable side effect profile and is recommended in

the 2018 AHA/ACC cholesterol guidelines as 2nd line therapy for LDL-C that remains ≥70 mg/dL despite being on a maximally tolerated statin.

Recommendation

It is recommended to add ezetimibe to the Texas HHS Psychiatric Drug Formulary.

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