



HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on January 28, 2022 via MS Teams. The meeting was called to order by Dr. Moron, Chair at 9:30 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Yekini Adeyemi, RN	Present	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	Present
Giovanna Betancourt, PharmD	Present	Rishi Sawhney, MD	Present
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	Absent	Patrick Young, MD	Present
Jeffery Matthews, MD	Present		

Guests Present: Tonya Barrios, State Hospitals Central Administration; Lisa Mican, PharmD, Austin State Hospital; Brett Knox, P4 PharmD Student, TX A&M; Josue Chaparro Zubia, P4 PharmD Student, UT Health East Texas; Kylie McNabb, P4 PharmD Student, UT Health East Texas

Opening

Introduction and Other Information

Annual Conflict of Interest Disclosures

A signed disclosure form has been received from each committee member. The committee reviewed one disclosed potential conflict made by a member that was on the speakers' bureau for a formulary product. The committee agreed that that member will refrain from participating in discussions or voting on any actions regarding that medication.

Review of Minutes

The minutes from the October 15, 2021 meeting were approved as previously distributed.

Unfinished Business

Prescription Digital Therapeutics

Angela Babin and Dr. Fitzwater reported Texas HHSC Medicaid services doesn't cover any digital applications at this time. The committee agreed to close this item and will revisit in the future if needed.

New Business

Adverse Drug Reaction Reports

The committee discussed two adverse drug reaction reports that were received from the field. These adverse events were reported to the FDA's MedWatch program.

ADR: fluoxetine, ibuprofen/bleeding

A 65-year-old Hispanic female diagnosed with schizophrenia, major neurocognitive disorder, borderline intellectual functioning, history of hypoxic encephalopathy (2011), hypertension, GERD, diabetes, obesity, Harvoni (course completed). Patient was continued on fluoxetine 40mg daily, ibuprofen 600mg three times daily, furosemide 20mg daily, Haldol decanoate 150mg every 28 days, lisinopril 5mg daily, metformin 1000mg twice daily, mirtazapine 30mg daily, olanzapine 20mg twice daily, empagliflozin 25mg daily, pioglitazone 45mg daily, Miralax 17 grams daily, ramelteon 8mg daily, Vitamin D 50,000 units every 14 days, Tramadol 50mg once daily on 8/27/21 and 8/28/21. On 8/3/21, hemoglobin (hgb) 13g/dL, hematocrit (hct) 40%. On 8/20/21, the patient fell and fractured her left humerus while trying to sit on the toilet. The orthopedic surgeon placed her in a sling and originally scheduled surgery for 8/30/21. On 8/24/21, hgb 8.6g/dL, hct 26%, aspirin was discontinued. On 8/25/21, she was noted to have increased upper arm swelling from shoulder to fingertips, bleeding into soft tissue. On 8/26/21, patient had two pieces surgically fixed with plate and screws and was transferred from community hospital to the gero-psych ward. On 8/30/21, hgb 6.1g/dL, hct 19.6%, patient was sent to ER for 2 units of packed red blood cells. Fluoxetine and ibuprofen were discontinued. On 8/31/21, hgb 9.7g/dL, hct 30.4%.

ADR: empagliflozin/extreme hyperglycemia

A 68-year-old Hispanic male admitted to the state hospital from jail on 2/3/21. Patient diagnosed with major neurocognitive disorder due to multiple causes, history of CVA with left sided weakness, type 2 diabetes mellitus (DM), BPH (foley), CAD, presence of stent of CABG (remote), porcine heart valve, angina, hypertension, hyperlipidemia, TBI, positive COVID test on 1/2/21. At the time of admission, the only DM medication patient was taking was metformin 1000mg twice daily. On admission, his diet was changed from regular American Diabetes Association (ADA) 2500 kcal with low sodium to 1800 kcal ADA solid with bedtime snack. On 2/4/21, A1c = 6.2%. On 2/12/21, foley was removed but within a week, patient was

hospitalized at the local community hospital for pyelonephritis and foley was reinserted. During this time, the patient also developed acute kidney injury which necessitated temporarily stopping metformin and using sliding scale insulin from 2/17/21 – 2/26/21. On 2/26/2021, metformin 1000mg twice daily was restarted. On 5/4/21, A1c = 7.0%, glucose = 302 mg/dL, BUN = 22 mg/dL, Cr = 0.86 mg/dL. Empagliflozin 10mg daily was added to metformin. On 6/28/21 (lab not seen), glucose = 303 mg/dL, BUN = 39 mg/dL, Cr = 1.07 mg/dL. On 7/13/21, patient complained of fatigue, dizziness, and nausea, blood sugar = 728 mg/dL, BUN = 39 mg/dL, CR = 1.57 mg/dL, CO₂ = 26 mEq/L (24-31). Patient received 10 units of regular insulin and blood sugar decreased to 450 mg/dL. Patient urine had ketones, specific gravity = 1.038 (1.001-1.035). Patient was sent to ER of community hospital for hydration, and was diagnosed with UTI, no blood ketones. Patient returned to the state hospital the next morning. Empagliflozin 10 mg and metformin were discontinued because of volume depletion and dehydration. Metformin was later restarted and throughout rest of his psychiatric admission, DM was treated with insulin and metformin.

New Drug Applications

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

Deutetrabenazine (Austedo)

Presented by Dr. Hall. 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 deutetrabenazine and valbenazine to the formulary. These medications will be in reserve use status and added to a new section of the formulary- Central Nervous System Agents, Agents for Tardive Dyskinesia- VMAT-2 inhibitors. The Treatment Algorithm for Tardive Dyskinesia flow chart, presented at the April 2018 meeting, will be updated and serve as the guidelines for use.

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

Buprenorphine LAI (Sublocade)

Presented by Brett Knox, P4 PharmD Student. Please refer to Appendix B for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee recommended to decline to add Buprenorphine LAI (Sublocade) to the formulary at this time.

Dulaglutide (Trulicity)

Pend until April

Quarterly Non-Formulary Drug Justification Report

For the first quarter of fiscal year 2022 (September 2021 through November 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 first quarter of fiscal year 2022:

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

Drug Formulary Sectional Review

In reviewing the formulary drug listings for Nutritional Agents/Nutritional Supplements, Dementia/Miscellaneous CNS, and Migraine agents the following changes were approved:

- Nutritional Agents/Nutritional Supplements
 - Combine supplements with agents currently in Nutritional Agents
 - Folic acid- add names Vitamin B₉, Folate
 - Niacin-add Vitamin B₃, move to Antihyperlipidemics Agents
 - Vitamin D₃ – remove Brand names Calcitriol, Rocaltrol
 - ◇ add Chewable oral and Softgel, oral dosage forms
 - Add new listing: 1,25-dihydroxyvitamin D₃ (Calcitriol, Rocaltrol)
 - ◇ Capsule oral, Solution oral
 - Potassium Chloride – remove Capsule oral, and Injection, concentrate dosage forms
 - Iron salts with or without vitamins and/or other minerals (Hemocytel Plus, Niferex-150 Forte)- add Tablet, enteric coated, oral dosage form
 - Vitamin B Complex – combine all products into one entry “with or without other vitamins and/or minerals” (similar to the entry for combination iron products)
- Nutritional Supplements (to be combined with Nutritional Agents)
 - Fish oil – remove name Nature Made Fish Oil and move to Miscellaneous nutritional agents
 - Glucosamine - move to Miscellaneous nutritional agents
 - Magnesium L-lactate dihydrate (Mag-Tab SR) - move to Minerals, Trace Elements, and Electrolytes

- Melatonin - move to Miscellaneous nutritional agents
- Certification Process
 - Revise table to show information on available certifications, remove column showing certified product lines
- Agents for Migraine
 - Valproic Acid/Valproate (Depakene) – remove Capsule, Sprinkle oral and Tablet, oral dosage forms. Add- Capsule, oral and Solution, oral dosage forms
- Updated Cost Index of several items

The updated formulary will be posted on the PEFC website.

Other Formulary Changes

Antihyperlipedemics-replace niacin entry with listing in Nutritional Agents.

HHSC Psychotropic Medications Consent List Annual Review

The committee reviewed and approved the following changes to the list of psychotropic medications requiring consent:

- Remove Aventyl from the nortriptyline listing
- Add "Reserve" to the naltrexone listings
- Add Toprol XL to the metoprolol listing

The updated document will be posted on the PEFC website.

Antipsychotic Tier Schedule Annual Review

The committee reviewed and approved the 2022 HHSC Antipsychotic Tier Schedule.

Psychotropic Medication Audit Criteria & Guidelines Review

The committee reviewed and approved recommended revisions to the following audit criteria documents:

- Naltrexone (update to match Reserve Table changes made in October)
- Antipsychotics- Atypical
- Antipsychotics- Clozapine

Additionally, the committee discussed whether to include off-label indications on the audit criteria and guidelines documents and determined that including an exhaustive list would not be feasible. A statement will be added to the documents acknowledging that there are off-label indications for use that have supporting evidence for efficacy and that if a medication is prescribed for an off-label indication, documentation in the patient chart will be recommended,. Off-label indications will not be included in future audit criteria and guidelines document revisions.

The updated documents will be posted to the PEFC website.

Issues from the Chief Medical Officer, State Hospitals

No issues to report.

Issues from the Medical Services Coordinator, SSLCs

Dr. Shipley reported a resurgence of COVID cases in SSLC facilities, most likely due to the Omicron variant as there have been fewer hospitalizations than were seen in the initial stages of the pandemic. Facilities have used sotrovimab with success.

Drug Shortages, Recalls, and FDA Safety Communications

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

Shortages

Chlordiazepoxide:

Mylan discontinued chlordiazepoxide capsules in early-2021 which put a higher demand on the other generic manufacturers (Teva, Epic).

Sterile water for injection:

Single dose vials from numerous manufacturers are in short supply due to manufacturing delays and increased demand. Sterile water for injection is used to reconstitute Zyprexa IM and Geodon IM.

Lorazepam for injection: single dose vials from numerous manufacturers are in short supply due to increased demand.

Recalls

Irbesartan:

Lupin Pharmaceuticals is recalling all batches of irbesartan tablets and irbesartan and hydrochlorothiazide tablets because analysis revealed that certain tested active pharmaceutical ingredient (API) batches (but not finished product batches) were above the specification limit for the impurity, N-nitrosoirbesartan. N-nitrosoirbesartan impurity is a probable human carcinogen based on results from laboratory tests. Lupin has received no reports of illness that appear to relate to this issue.

Metformin ER:

Viona Pharmaceuticals is recalling multiple lots of metformin extended-release tablets, 750 mg due to the detection of N-nitrosodimethylamine (NDMA) in long-term stability samples. This product was manufactured by Cadila Healthcare Limited, Ahmedabad, India for U.S. distribution by Viona Pharmaceuticals Inc.

Senna syrup:

Lohxa is recalling one lot of senna syrup, 8.8 mg/5mL unit dose cups, due to microbial contamination. To date, Lohxa has not received any reports of adverse events related to this recall.

Safety-related Labeling Changes

Ondansetron (Zofran):

Newly added section. Myocardial ischemia has been reported in patients treated with ondansetron. In some cases, predominantly during intravenous administration, the symptoms appeared immediately after administration but resolved with prompt treatment. Coronary artery spasm appears to be the most common underlying cause. Therefore, monitor or advise patients for signs or symptoms of myocardial ischemia after oral administration of ondansetron.

Venlafaxine, desvenlafaxine (Effexor, Pristiq):

Addition to Warnings and Precautions underlined. There have been postmarketing reports of serious discontinuation symptoms which can be protracted and severe. Completed suicide, suicidal thoughts, aggression and violent behavior have been observed in patients during reduction in Effexor XR dosage, including during discontinuation. Other postmarketing reports describe visual changes (such as blurred vision or trouble focusing) and increased blood pressure after stopping or reducing the dose of Effexor XR. In some patients, discontinuation may need to occur over a period of several months.

Azithromycin (Zithromax):

Newly added information. Some observational studies have shown an approximately two-fold increased short-term potential risk of acute cardiovascular death in adults exposed to azithromycin relative to other antibacterial drugs, including amoxicillin. The five-day cardiovascular mortality observed in these studies ranged from 20 to 400 per million azithromycin treatment courses. This potential risk was noted to be greater during the first five days of azithromycin use and does not appear to be limited to those patients with preexisting cardiovascular diseases. The data in these observational studies are insufficient to establish or exclude a causal relationship between acute cardiovascular death and azithromycin use. Consider balancing this potential risk with treatment benefits when prescribing azithromycin.

Lumateperone (Caplyta):

Newly added information and revisions to boxed warning underlined.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. The safety and effectiveness of CAPLYTA have not been established in pediatric patients.

Brexpiprazole (Rexulti):

Additions and/or revisions underlined. Safety and effectiveness of REXULTI for treatment of schizophrenia have been established in pediatric patients 13 years of age and older. Use of REXULTI in this population is supported by evidence from adequate and well-controlled studies in adults with schizophrenia, pharmacokinetic data from adults and pediatric patients, and safety data in pediatric patients 13 to 17 years of age... Safety and effectiveness in pediatric patients with major depressive disorder have not been established.

Atomoxetine (Strattera):

Additions and/or revisions underlined. Patients with bipolar disorder or risk factors for bipolar disorder may be at increased risk of developing mania or mixed episodes during treatment with atomoxetine. It may not be possible to determine whether a manic or mixed episode that appears during treatment with atomoxetine is due to an adverse reaction to atomoxetine or a patient's underlying bipolar disorder. Before initiating treatment with atomoxetine, patients should be adequately screened for risk factors for bipolar disorder such as a personal or family history of mania and depression.

Patients beginning treatment with atomoxetine should be monitored for the appearance or worsening of aggressive behavior or hostility. There is evidence that atomoxetine may cause the emergence or worsening of aggressive behavior or hostility. ADHD and other mental illnesses can be associated with irritability, which can make it difficult to determine if the drug or the underlying psychiatric condition is causing the emergence or worsening of aggressive behavior or hostility in specific patients. If such symptoms occur during treatment, consider a possible causal role of atomoxetine.

Buprenorphine (Subutex, Suboxone):

Drug Safety Communication: The FDA is warning that dental problems have been reported with medicines containing buprenorphine that are dissolved in the mouth, specifically tablets and films dissolved under the tongue or placed against the inside of the cheek. The dental problems, including tooth decay, cavities, oral infections, and loss of teeth, can be serious and have been reported even in patients with no history of dental issues. Despite these risks, buprenorphine is an important treatment option for opioid use disorder (OUD) and pain, and the benefits of these medicines clearly outweigh the risks.

The FDA is requiring a new warning about the risk of dental problems be added to the prescribing information and the patient Medication Guide for all buprenorphine-containing medicines dissolved in the mouth.

Open Forum

Next Meeting Date

The next meeting is scheduled for April 22, 2022.

Adjourn

There being no further business, the meeting was adjourned at 3:30 p.m.

Approved: *David Moron*

David Moron, MD, Chairman

Minutes Prepared by:

Tonya Barrios, PhTR

Reviewed by:

Jean Baemayr, PharmD

Appendix A

Deutetrabenazine (Austedo)

Classification

Central Nervous System Agent

Pharmacology

Vesicular monoamine transporter 2 (VMAT2) is a protein that regulates the packaging and release of monoamines (dopamine, serotonin, norepinephrine, and histamine). VMAT2 inhibitors decrease monoamine uptake into the synaptic vesicles, thereby reducing neurotransmitter release into the synapse. Available reversible VMAT2 inhibitors include tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza). Deutetrabenazine is the deuterium substituted form of tetrabenazine. Deuterium (aka heavy hydrogen) is a hydrogen isotope that forms strong bonds with carbon which slow down deutetrabenazine's metabolism. Compared to tetrabenazine, deutetrabenazine has a longer half-life, decreased plasma fluctuations and fewer adverse effects associated with peak concentrations (somnolence, depression, insomnia, akathisia, parkinsonism). Deutetrabenazine undergoes extensive hepatic metabolism to its active deuterated metabolites-- α -dihydrodeutetrabenazine [HTBZ] and β -HTBZ.

Black Box Warning for Depression and Suicidality in Patients with Huntington's Disease

Deutetrabenazine (Austedo) can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of deutetrabenazine (Austedo) must balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior. Patients, their caregivers, and families should be informed of the risk of depression and suicidality and should be instructed to report behaviors of concern promptly to the treating physician. Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington's disease. Deutetrabenazine (Austedo) is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression.

Indication

- Chorea associated with Huntington's disease
- Tardive dyskinesia

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	About 80% absorbed. After oral dosing, deutetrabenazine plasma concentrations are generally below the limit of detection. Peak plasma concentrations (C_{max}) of deuterated α -HTBZ and β -HTBZ reached within 3 to 4 hours. C_{max} increased approximately 50% in presence of food
Distribution	Median volume of distribution of α -HTBZ and β -HTBZ = 500 L, 730 L, respectively From PET studies, following IV injection of ^{11}C -labeled tetrabenazine, radioactivity rapidly distributed to the brain. Highest binding in the striatum, lowest binding in the cortex
Metabolism	Extensively biotransformed (carbonyl reductase) to major active metabolites-- α -dihydro-tetrabenazine [HTBZ] and β -HTBZ, which are then metabolized primarily by CYP2D6, with minor contributions of CYP1A2 and CYP3A4/5, to form several minor metabolites
Excretion	Primarily renal. Half-life of total ($\alpha + \beta$)-HTBZ = 9 to 10 hours

Dosage/Administration

The dose of deutetrabenazine (Austedo) is determined individually for each patient based on reduction of chorea or tardive dyskinesia and tolerability. The package insert contains specific dosing instructions about switching patients from tetrabenazine (Xenazine) to deutetrabenazine (Austedo). When first prescribed to patients who are not being switched from tetrabenazine, the recommended starting dose of deutetrabenazine (Austedo) is 6 mg administered orally once daily for patients with Huntington's disease and 12 mg per day (6 mg twice daily) for patients with tardive dyskinesia. The dose of deutetrabenazine (Austedo) may be increased at weekly intervals in increments of 6 mg per day to a maximum recommended daily dosage of 48 mg. Administer total daily dosages of 12 mg or above in two divided doses. Administer deutetrabenazine (Austedo) with food. Swallow deutetrabenazine (Austedo) whole. Do not chew, crush, or break tablets.

Dosage Adjustment with Strong CYP2D6 Inhibitors. In patients receiving strong CYP2D6 inhibitors (e.g., quinidine, paroxetine, fluoxetine, bupropion), the total daily dosage of deutetrabenazine (Austedo) should not exceed 36 mg (maximum single dose of 18 mg).

Dosage Adjustment in Poor CYP2D6 Metabolizers. In patients who are poor CYP2D6 metabolizers, the total daily dosage of deutetrabenazine (Austedo) should not exceed 36 mg (maximum single dose of 18 mg).

Discontinuation and Interruption of Treatment. Treatment with deutetrabenazine (Austedo) can be discontinued without tapering. Following treatment interruption of greater than one week, deutetrabenazine (Austedo) therapy should be re-titrated when resumed. For treatment interruption of less than one week, treatment can be resumed at the previous maintenance dose without titration.

Use in Special Population

Pregnancy

Risk Summary: There are no adequate data on the developmental risk associated with the use of deutetrabenazine (Austedo) in pregnant women. Administration of deutetrabenazine to rats during organogenesis produced no clear adverse effect on embryofetal development. However, administration of tetrabenazine to rats throughout pregnancy and lactation resulted in an increase in stillbirths and postnatal offspring mortality.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation

Risk Summary: There are no data on the presence of deutetrabenazine or its metabolites in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for deutetrabenazine (Austedo) and any potential adverse effects on the breastfed infant from Austedo or from the underlying maternal condition.

Pediatric Use

Tourette syndrome

The safety and effectiveness of Austedo have not been established in pediatric patients for the treatment of Tourette syndrome.

Chorea associated with Huntington's disease and Tardive dyskinesia

The safety and effectiveness of Austedo have not been established in pediatric patients for the treatment of chorea associated with Huntington's disease or for the treatment of tardive dyskinesia.

Geriatric Use

Clinical studies of Austedo did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should

be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of hepatic, renal, and cardiac dysfunction, and of concomitant disease or other drug therapy.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of deutetrabenazine and its primary metabolites has not been studied; however, in a clinical study conducted with tetrabenazine, a closely related VMAT2 inhibitor, there was a large increase in exposure to tetrabenazine and its active metabolites in patients with hepatic impairment. The clinical significance of this increased exposure has not been assessed, but because of concerns for a greater risk for serious adverse reactions, the use of Austedo in patients with hepatic impairment is contraindicated.

Poor CYP2D6 Metabolizers

Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme, it is likely that the exposure to α -HTBZ and β -HTBZ would be increased similarly to taking a strong CYP2D6 inhibitor (approximately 3-fold). In patients who are CYP2D6 poor metabolizers, the daily dose of Austedo should not exceed 36 mg (maximum single dose of 18 mg).

Contraindication

Patients with Huntington's disease who are suicidal or have untreated or inadequately treated depression. Patients with hepatic impairment. Taking reserpine. At least 20 days should elapse after stopping reserpine before starting deutetrabenazine (Austedo). Taking monoamine oxidase inhibitors (MAOIs). Deutetrabenazine (Austedo) should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Taking tetrabenazine (Xenazine) or valbenazine.

Precautions

Depression and Suicidality in Patients with Huntington's Disease

Patients with Huntington's disease are at increased risk for depression, and suicidal ideation or behaviors (suicidality). Deutetrabenazine (Austedo) may increase the risk for suicidality in patients with Huntington's disease. In a 12-week, double-blind, placebo-controlled trial, suicidal ideation was reported by 2% of patients treated with deutetrabenazine (Austedo), compared to no patients on placebo; no suicide attempts and no completed suicides were reported. Depression was reported by 4% of patients treated with deutetrabenazine (Austedo). When considering the use of deutetrabenazine (Austedo), the risk of suicidality should be balanced against the need for treatment of chorea. All patients treated with deutetrabenazine (Austedo) should be observed for new or worsening depression or suicidality. If depression or suicidality does not resolve, consider discontinuing treatment with deutetrabenazine (Austedo). Patients, their caregivers, and families should be informed of the risks of

depression, worsening depression, and suicidality associated with deutetrabenazine (Austedo), and should be instructed to report behaviors of concern promptly to the treating physician. Patients with Huntington's disease who express suicidal ideation should be evaluated immediately.

Clinical Worsening and Adverse Events in Patients with Huntington's Disease

Huntington's disease is a progressive disorder characterized by changes in mood, cognition, chorea, rigidity, and functional capacity over time. VMAT2 inhibitors, including Austedo, may cause a worsening in mood, cognition, rigidity, and functional capacity. Prescribers should periodically re-evaluate the need for Austedo in their patients by assessing the effect on chorea and possible adverse effects, including sedation/somnolence, depression and suicidality, parkinsonism, akathisia, restlessness, and cognitive decline. It may be difficult to distinguish between adverse reactions and progression of the underlying disease; decreasing the dose or stopping the drug may help the clinician to distinguish between the two possibilities. In some patients, the underlying chorea itself may improve over time, decreasing the need for Austedo.

QTc Prolongation

Austedo may prolong the QT interval, but the degree of QT prolongation is not clinically significant when Austedo is administered within the recommended dosage range. Austedo should be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission. While NMS has not been observed in patients receiving Austedo, it has been observed in patients receiving tetrabenazine (a closely related VMAT2 inhibitor). Clinicians should be alerted to the signs and symptoms associated with NMS. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnosis of NMS can be complicated; other serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal disorders can present with similar signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology. The management of NMS should include (1) immediate discontinuation of Austedo; (2)

intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. Recurrence of NMS has been reported with resumption of drug therapy. If treatment with Austedo is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Akathisia, Agitation, and Restlessness

Austedo may increase the risk of akathisia, agitation, and restlessness in patients with Huntington's disease and tardive dyskinesia. In a 12-week, double-blind, placebo-controlled trial in Huntington's disease patients, akathisia, agitation, or restlessness was reported by 4% of patients treated with Austedo, compared to 2% of patients on placebo; in patients with tardive dyskinesia, 2% of patients treated with Austedo and 1% of patients on placebo experienced these events. Patients receiving Austedo should be monitored for signs and symptoms of restlessness and agitation, as these may be indicators of developing akathisia. If a patient develops akathisia during treatment with Austedo, the Austedo dose should be reduced; some patients may require discontinuation of therapy.

Parkinsonism

Austedo may cause parkinsonism in patients with Huntington's disease or tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. Because rigidity can develop as part of the underlying disease process in Huntington's disease, it may be difficult to distinguish between potential drug-induced parkinsonism and progression of underlying Huntington's disease. Drug-induced parkinsonism has the potential to cause more functional disability than untreated chorea for some patients with Huntington's disease. Postmarketing cases of parkinsonism in patients treated with Austedo for tardive dyskinesia have been reported. Signs and symptoms in reported cases have included bradykinesia, gait disturbances, which led to falls in some cases, and the emergence or worsening of tremor. In most cases, the development of parkinsonism occurred within the first two weeks after starting or increasing the dose of Austedo. In cases in which follow-up clinical information was available, parkinsonism was reported to resolve following discontinuation of Austedo therapy. If a patient develops parkinsonism during treatment with Austedo, the Austedo dose should be reduced; some patients may require discontinuation of therapy.

Sedation and Somnolence

Sedation is a common dose-limiting adverse reaction of Austedo. In a 12-week, double-blind, placebo-controlled trial examining patients with Huntington's disease, 11% of Austedo-treated patients reported somnolence compared with 4% of patients on placebo and 9% of Austedo-treated patients reported fatigue compared with 4% of placebo-treated patients. Patients should not perform activities requiring mental alertness to maintain the safety of themselves or others, such as operating a motor

vehicle or operating hazardous machinery, until they are on a maintenance dose of Austedo and know how the drug affects them.

Hyperprolactinemia

Serum prolactin levels were not evaluated in the Austedo development program. Tetrabenazine, a closely related VMAT2 inhibitor, elevates serum prolactin concentrations in humans. Following administration of 25 mg of tetrabenazine to healthy volunteers, peak plasma prolactin levels increased 4- to 5-fold. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if Austedo is being considered for a patient with previously detected breast cancer. Although amenorrhea, galactorrhea, gynecomastia, and impotence can be caused by elevated serum prolactin concentrations, the clinical significance of elevated serum prolactin concentrations for most patients is unknown. Chronic increase in serum prolactin levels (although not evaluated in the Austedo or tetrabenazine development programs) has been associated with low levels of estrogen and increased risk of osteoporosis. If there is a clinical suspicion of symptomatic hyperprolactinemia, appropriate laboratory testing should be done and consideration should be given to discontinuation of Austedo.

Binding to Melanin-Containing Tissues

Since deutetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that Austedo may cause toxicity in these tissues after extended use. Neither ophthalmologic nor microscopic examination of the eye has been conducted in the chronic toxicity studies in a pigmented species such as dogs. Ophthalmologic monitoring in humans was inadequate to exclude the possibility of injury occurring after long-term exposure. The clinical relevance of deutetrabenazine's binding to melanin-containing tissues is unknown. Although there are no specific recommendations for periodic ophthalmologic monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Adverse Effects

The data described below reflect 410 tardive dyskinesia patients participating in clinical trials. Austedo was studied primarily in two 12-week, placebo-controlled trials (fixed dose, dose escalation). The population was 18 to 80 years of age and had tardive dyskinesia and had concurrent diagnoses of mood disorder (33%) or schizophrenia/schizoaffective disorder (63%). In these studies, Austedo was administered in doses ranging from 12-48 mg per day. All patients continued on previous stable regimens of antipsychotics; 71% and 14% respective atypical and typical antipsychotic medications at study entry.

The most common adverse reactions occurring in greater than 3% of Austedo-treated patients and greater than placebo were nasopharyngitis and insomnia. The adverse

reactions occurring in >2% or more patients treated with Austedo (12-48 mg per day) and greater than in placebo patients in two double-blind, placebo-controlled studies in patients with tardive dyskinesia (Study 1 and Study 2) are summarized in the table below.

Adverse Reaction	Austedo n = 279 (%)	Placebo n = 131 (%)
Nasopharyngitis	4	2
Insomnia	4	1
Depression/dysthymic disorder	2	1
Akathisia/agitation/restlessness	2	1

One or more adverse reactions resulted in a reduction of the dose of study medication in 4% of Austedo treated patients and in 2% of placebo-treated patients.

Monitoring

Electrolytes; EKG (QT interval before and after dose is increased to > 24 mg/day in patients with increased risk for QTc prolongation); signs/symptoms of depression or suicidal ideation; signs and/or symptoms of NMS, restlessness and agitation

Interactions

Strong CYP2D6 Inhibitors

A reduction in Austedo dose may be necessary when adding a strong CYP2D6 inhibitor in patients maintained on a stable dose of Austedo. Concomitant use of strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion) has been shown to increase the systemic exposure to the active dihydro-metabolites of deutetrabenazine by approximately 3-fold. The daily dose of Austedo should not exceed 36 mg per day, and the maximum single dose of Austedo should not exceed 18 mg in patients taking strong CYP2D6 inhibitors.

Reserpine

Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Prescribers should wait for chorea or dyskinesia to reemerge before administering Austedo to help reduce the risk of overdose and major depletion of serotonin and norepinephrine in the central nervous system. At least 20 days should elapse after stopping reserpine before starting Austedo. Austedo and reserpine should not be used concomitantly.

Monoamine Oxidase Inhibitors (MAOIs)

Austedo is contraindicated in patients taking MAOIs. Austedo should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI.

Neuroleptic Drugs

The risk of parkinsonism, NMS, and akathisia may be increased by concomitant use of Austedo and dopamine antagonists or antipsychotics.

Alcohol or Other Sedating Drugs

Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence.

Concomitant Tetrabenazine or Valbenazine

Austedo is contraindicated in patients currently taking tetrabenazine or valbenazine. Austedo may be initiated the day following discontinuation of tetrabenazine.

Efficacy

Aim to Reduce Movements in Tardive Dyskinesia (ARM-TD)

Methods

In a 12-week, randomized, double-blind, multicenter trial, 117 patients with moderate to severe TD received deutetrabenazine (n = 58) or placebo (n = 59). Inclusion criteria included an Abnormal Involuntary Movement Scale (AIMS) score ≥ 6 , stable psychiatric illness, and stable psychoactive medication treatment. Study subjects had a TD diagnosis for ≥ 3 months before screening and had been treated with dopamine receptor antagonists (DRA) for ≥ 3 months (≥ 1 month if age ≥ 60 years).

Exclusion criteria included treatment with any of the following medications within 30 days: tetrabenazine, reserpine, alpha-methyl-p-tyrosine, strong anticholinergic medications, metoclopramide, dopamine agonists, levodopa, stimulants. Other exclusion criteria included treatment with botulinum toxin within three months of study initiation, presence of a neurologic condition that could confound TD assessments, serious untreated or undertreated psychiatric illness, unstable medical illness, history of active SI/behavior within 6 months, score ≥ 11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS), QT_c > 450 msec in men, > 460 msec in women.

At baseline, patients were stratified by use of DRA. The initial dose of deutetrabenazine was 12 mg/d (6 mg bid). For the first six weeks of the study, the dose was titrated weekly by 6 mg/d until adequate dyskinesia control was achieved, a significant AE occurred, or the max dose (48 mg/d) was reached. Patients then entered a six-week maintenance phase followed by a one-week washout. AIMS exams were performed at weeks 2, 4, 6, 9, 12, and 13. Investigators performed

EKGS at baseline and weeks 2 and 12 for all patients. Patients receiving other QT-prolonging meds also had ekgs at weeks 4, 6, and 9.

Results

Both groups had similar demographics and baseline characteristics. Roughly 70% of study subjects had been diagnosed with schizophrenia or schizoaffective disorder, 23.1% had bipolar disorder, and 25.6% had depression. Most (80.3%) were being treated with a DRA at baseline and throughout the study. At the end of the six-week dose titration phase and throughout the maintenance phase, the mean (SD) total daily dose was 38.8 (7.92) mg/d. The patient baseline characteristics by treatment group are shown in the table below.

	Deutetrabenazine (n = 58)	Placebo (n = 59)
Patient demographics		
Age (SD), y	55.9 (9.8)	53.3 (10.6)
Female, n (%)	29 (50.0)	32 (54.2)
White, n (%)	37 (63.8)	44 (74.6)

	Deutetrabenazine (n = 58)	Placebo (n = 59)
Clinical characteristics		
Duration of TD, mo	72.6 (81.7)	76.8 (82.1)
AIMS score, items 1-7 (SD)	9.6 (4.1)	9.6 (3.8)

	Deutetrabenazine (n = 58)	Placebo (n = 59)
Most common AP used at BL, n (%)		
Quetiapine	14 (24.1)	18 (30.5)
Risperidone	9 (15.5)	7 (11.9)
Olanzapine	8 (13.8)	5 (8.5)

Most common AP used at BL, n (%)	Deutetrabenazine (n = 58)	Placebo (n = 59)
Trazodone	9 (15.5)	10 (16.9)
Bupropion	5 (8.6)	6 (10.2)
Sertraline	6 (10.3)	4 (6.8)
Citalopram	5 (8.6)	5 (8.5)

From baseline to week 12, deutetrabenazine significantly reduced AIMS scores compared with placebo. **Least squares mean (SE) -3.0 (0.45) versus -1.6 (0.46), p = 0.019.**

The incidence of depression/depressed mood and suicidal ideation in the deutetrabenazine group was similar to or lower than that in the placebo group.

Side effect	Deutetrabenazine (n = 58), n (%)	Placebo (n = 59), n (%)
Depressed mood	1 (1.7)	0 (0.0)
Depression	0 (0.0)	1 (1.7)
Suicidal ideation	0 (0.0)	1 (1.7)
Somnolence	8 (13.8)	6 (10.2)
Insomnia	4 (6.9)	1 (1.7)
Akathisia	3 (5.2)	0 (0.0)
Anxiety	2 (3.4)	4 (6.8)

Small reductions in parkinsonism severity (Unified Parkinson’s Disease Rating Scale) were observed in both groups (deutetrabenazine mean change = - 0.9 (8.09), placebo mean change = - 3.8 (7.87). There were no significant differences in QTc interval prolongation between groups (p = 0.153). One placebo treated patient had Qtc > 500 msec.

The authors concluded that, in patients with TD, deutetrabenazine was well tolerated and significantly reduced abnormal movements.

Long-term safety and efficacy of deutetrabenazine for the treatment of TD

Fernandez and colleagues conducted a 106 week, open-label, single-arm extension study of patients who successfully completed the two, 12-week phase 3 trials (ARM-TD and AIM-TD, n = 368). Successful completion was defined as participation through week 13, compliance with study drug and procedures, and the absence of serious adverse effects.

Study subjects (n = 343) were washed out from their phase 3 study drug (deutetrabenazine [n = 232] or placebo [n = 111]) for at least one week. All then started deutetrabenazine 12 mg/day (6 mg bid). For six weeks, the dose was increased weekly by 6 mg/day until adequate dyskinesia control was achieved with good tolerability. Max total daily dosage was 48 mg/day. The max dose for patients taking strong CYP2D6 inhibitors (paroxetine, fluoxetine or bupropion) was 36 mg/day.

Mean duration of deutetrabenazine treatment was 352.9 days. 76% (259/343) of patients were treated for at least 54 weeks and 20% (69/343) were treated for at least 80 weeks. Improvements in AIMS scores were noted by week 2; continued improvement was seen through Week 106 in the patients who remained in the study. The mean (SE) change in AIMS score was -4.9 (0.4) at Week 54 (n = 146), -6.3 (0.7) at Week 80 (n = 66) and -5.1 (2.0) at Week 106 (n = 8).

The most common adverse events were anxiety, somnolence and depression; most of these were mild or moderate in severity. Investigators calculated exposure-adjusted incidence rates (EAIRs) by adjusting the incidence of AEs for the duration of treatment exposure. This was done to compare adverse event frequencies in the long-term extension study with those in the short-term trials (ARM-TD and AIM-TD). EAIRs during the long-term extension study for depression, anxiety, suicidality, akathisia, somnolence, and parkinsonism were similar to or lower than those observed in the shorter studies, implying no evidence of cumulative toxicity or tolerability issues despite the longer treatment period.

Three patients had serious adverse events possibly related to deutetrabenazine: intentional overdose/suicide attempt, exacerbation of mania and exacerbation of hypomania. The patient who experienced intentional overdose and suicide attempt had a history of depression, bipolar disorder, anxiety, and suicide attempts and was on 18 mg per day of deutetrabenazine.

6/343 (2%) of patients had a post-baseline QTc > 480 msec, 3/343 (< 1%) had a post-baseline QTc > 500 msec.

Dosage Forms/Cost

All info from GoodRX, Walgreens
 Austedo 6 mg, #60 = \$4,235.13
 Austedo 9 mg, # 60 = \$4,763.52
 Austedo 12 mg, #60 = \$6,348.91

Attributes	Valbenazine (Ingrezza)	Deutetrabenazine (Austedo)	Tetrabenazine (Xenazine)
Dosing	40 mg po daily-am, increase to 80 mg/day after 1 week. A dosage of 40 mg or 60 mg once daily may be considered depending on response and tolerability	6 mg po qday, increase weekly in 6 mg/day increments as tolerated to a maximum of 48 mg/day; doses > 12 mg should be divided into 2 doses	12.5-100 mg in divided doses 3 times per day
Dose adjustment	Liver impairment/strong CYP2D6/3A4 inhibitors and poor CYP2D6 metabolizers: maximum daily dose of 40 mg	Strong CYP2D6 inhibitors/poor metabolizers: maximum daily dose of 36 mg, maximum single dose of 18 mg	Strong CYP2D6 inhibitors/poor metabolizers; maximum daily dose of 50 mg, maximum single dose of 25 mg
Drug interactions	Avoid use with MAOIs and strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, St John's wort)	Avoid use with MAOIs; monitor QTc interval in patients taking > 24 mg/day who are also on other QTc-prolonging medications	Avoid use with MAOIs
Adverse effects	Somnolence, dry mouth, akathisia, headache, uti	Somnolence, dry mouth, akathisia, headache, anxiety, QTc prolongation (rare), depression in patients with Huntington's disease	Somnolence, fatigue, insomnia, anxiety, nausea, depression in patients with Huntington's disease

Attributes	Valbenazine (Ingrezza)	Deutetrabenazine (Austedo)	Tetrabenazine (Xenazine)
Contraindications	No contraindications but avoid in patients with impaired renal function or who are pregnant or breast-feeding	Contraindicated in patients with hepatic impairment and patients with suicidal ideation or untreated/inadequately treated depression	Contraindicated in patients with suicidal ideation or untreated/inadequately treated depression
Special information	None noted	Black box warning for increased risk of depression and suicidality in patients with Huntington's disease	Black box warning for increased risk of depression and suicidality in patients with Huntington's disease

Khorassani 2021. Comparison of VMAT2 Inhibitors. A Carlat Psychiatry Reference Table.

Summary/Conclusion

In 2017, the FDA approved the first treatments for TD in adults--valbenazine (Ingrezza) and deutetrabenazine (Austedo). In April 2018, the PEFC reviewed valbenazine (Ingrezza) and recommended that it remain non-formulary, even though the updated American Academy of Neurology (AAN) guideline (Bhidayasiri R, et al., 2018) had just declared valbenazine (Ingrezza) and deutetrabenazine (Austedo) the first and only effective treatments (Level A recommendation) for TD. This decision was based on our system's limited resources and the fact that valbenazine's (Ingrezza) average AIMS reductions were not drastically different from those seen with non-approved treatments. In the Kinect 3 study, six weeks of treatment with valbenazine 80 mg per day reduced AIMS scores an average of 3.2 points. However, smaller, lower quality studies showed an average reduction of 2.13 points for ginkgo biloba and that clonazepam is probably effective in the short term (both Level B, probably effective). Studies with amantadine (Level C, possibly effective) showed average reductions of about 2 points in patients who improved while trials of controlled-release melatonin (Level U, insufficient evidence) demonstrated average reductions of 2.45 points. In April 2018, the committee approved an algorithm for the treatment of tardive dyskinesia, monitoring parameters, and a dosing table. See attached. The algorithm shows valbenazine (Ingrezza) as a last-line agent, only to be used after trials of all other treatment options.

Since the approval of the VMAT2 inhibitors in 2017, there has been a reappraisal of best practices for recognizing and managing TD. A recent consensus statement and the third edition of the APA Practice Guideline for the Treatment of Patients with

Schizophrenia (2020) provide guidance on the screening, diagnosis, and treatment of TD.

In late 2017-early 2018, a group of TD experts used a modified Delphi method to develop recommendations concerning screening, diagnosis, and treatment of tardive dyskinesia. The consensus statement provides guidance on best practices including routine monitoring procedures adaptable to clinical settings, diagnosing mild cases of TD, and implementing a comprehensive strategy that incorporates patient and caregiver input, review of antipsychotic and anticholinergic medications, indications for VMAT2 inhibitors, and appropriate follow-up.

The 2020 APA Practice Guideline for the Treatment of Patients with Schizophrenia states that most patients with TD have mild symptoms but some patients' symptoms can be described as moderate or severe and that in these cases, clinicians look for other contributors to a movement disorder. This assessment would include a neurological examination, complete history of motor symptoms, past and current medications, laboratory testing. Depending on the results, additional studies might be indicated (ceruloplasmin for Wilson's disease, brain MRI, lumbar puncture). If dyskinesias have begun or increased during antipsychotic dose reduction, their course should be tracked for several months because spontaneous reductions or resolution may occur. If no contributing cause is identified and moderate to severe or disabling tardive dyskinesia persists, treatment is recommended (1B) with a reversible VMAT2 inhibitor. The guideline also recommends that VMAT2 inhibitors be considered for patients with mild tardive dyskinesia based on TD associated impairment, effect on psychosocial functioning and patient preference.

Compared to valbenazine (Ingrezza), deutetrabenazine (Austedo) has a more complicated titration (seven versus three dosing options). Valbenazine (Ingrezza) has the advantage of once daily dosing while deutetrabenazine requires BID administration with food. Deutetrabenazine's multiple dosing options may target a wider range of VMAT2 occupancy. VMAT2 occupancies for deutetrabenazine at doses between 6 mg and 42 mg range between 51% and 92%; VMAT2 occupancies for valbenazine at doses between 40 mg and 80 mg range between 84% and 91%. Individual patients might require different degrees of VMAT2 inhibition to achieve the best balance between efficacy and tolerability and Caroff et al. recommend that if one VMAT2 inhibitor is ineffective or not tolerated, the next step is to switch to another VMAT2 inhibitor before using other agents.

Recommendation

Add both deutetrabenazine (Austedo) and valbenazine (Ingrezza) to the formulary as reserve agents. With regard to the recognition and management of TD, recommendations found in resources such as the APA guideline and Caroff et al may help clinicians identify patients who would benefit from VMAT2 inhibitor therapy.

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Appendix B

Buprenorphine (Sublocade®) Subcutaneous Injection, CIII Classification

Partial opioid agonist

Pharmacology [1]

Sublocade® (buprenorphine extended-release) injection, for subcutaneous use is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor.

Indication- FDA

FDA Approved: Sublocade® is indicated for patients with moderate to severe opioid use disorder that have been on a stable dose of buprenorphine treatment for a minimum of seven days.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Subcutaneous injection of either a 100 mg or 300 mg dose in adults has a mean absolute bioavailability of 2.87% and 2.11%, respectively. Median T_{max} occurred in 24 hours; mean C_{max} for either a 100 mg or 300 mg dose is 5.10 ng/mL and 11.81 ng/mL, respectively; mean AUC 126.2 ng·hr/mL.
Distribution	96% protein bound, primarily to alpha and beta globulin.
Metabolism	Primarily metabolized CYP3A4 to norbuprenorphine. This metabolite can be subject to additional glucuronidation and binds to opioid receptors but has not been clinically studied for opioid-like activity.
Excretion	In urine, most of buprenorphine and norbuprenorphine were conjugated and in feces almost all of the buprenorphine and norbuprenorphine were unconjugated. Almost all of the dose was accounted for between buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites.

Dosage/Administration

- For initiation of treatment following induction, the recommended dose of Sublocade® (buprenorphine extended release) is 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly. The maintenance dose may be increased to 300 mg monthly for patients who tolerate the 100 mg dose, but do not demonstrate a satisfactory clinical response, as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use.

- For initiation of treatment in patients established on long-term treatment with transmucosal buprenorphine whose symptoms are controlled:
 - 8-18 mg/day transmucosal buprenorphine
 - Injection #1: 300 mg
 - Injection #2: 100 mg
 - Maintenance dose: 100 mg
 - For those experiencing craving or withdrawal symptoms after the initial 300 mg dose, use of 300 mg as the second dose may be considered
 - 20-24 mg/day transmucosal buprenorphine
 - Injection #1: 300 mg
 - Injection #2: 300 mg
 - Maintenance dose: 100 mg
- Sublocade® (buprenorphine extended-release) injection, for subcutaneous use is stored in refrigeration between 2 and 8°C (35.6 and 46.4°F) and administered by the subcutaneous route on the abdomen only via syringe using a 19 gauge, 5/8" needle.
- Only healthcare providers should prepare and administer Sublocade
- A patient who misses a dose should receive the next dose as soon as possible. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect. Administer Sublocade monthly with a minimum of 26 days between doses.
- Initiate Sublocade treatment only following induction and dose-adjustment with a transmucosal buprenorphine-containing product.
- Administer each injection only using the syringe and safety needle included with the product. To avoid irritation, rotate subcutaneous injection sites on the abdomen between the transpyloric and transtuberular planes.
- Remove Sublocade from refrigeration at least 15 minutes before administration but discard if left at room temperature >7 days.
- Do not remove from foil pouch and attach needle until patient arrives at time of administration.

Use in Special Population

Pregnancy

Data from randomized clinical trials studying the link between buprenorphine exposure and fetal malformations are limited but current data does not suggest an increased risk of major malformations specifically due to buprenorphine exposure. Animal data suggests that the vehicle in Sublocade, NMP, is largely responsible for visceral and skeletal malformations but that buprenorphine may be partially contributing to these effects as well. Notably, the doses of Sublocade administered to rats and rabbits in the animal studies were 38 and 15 times the maximum relative dose recommended for human use. Advise pregnant women and women of childbearing age of the potential risk to the fetus.

Lactation

Buprenorphine and its metabolite norbuprenorphine are excreted in human milk and have been found in infant urine. The mother is advised to monitor the infant for increased drowsiness and breathing difficulties if taking buprenorphine while nursing. Potential risk to breastfed infants should be considered along with mother's clinical need for the medication.

Pediatric Use

Safety and effectiveness of Sublocade® (buprenorphine extended-release) injection, for subcutaneous use in pediatric patients has not been established.

Females and Males of Reproductive Potential

Females and males of reproductive potential may experience reduced fertility with chronic use of opioids and should be counseled about this possibility while using Sublocade.

Geriatric Use

Studies utilizing Sublocade® (buprenorphine extended-release) injection, for subcutaneous use did not include sufficient numbers of adults aged 65 years and older, resulting in an inability to state whether they respond differently than younger adults. Caution should be taken when prescribing Sublocade to individuals over the age of 65 due to increased likelihood of renal, hepatic, or cardiac dysfunction. Patients in this group should be closely monitored for signs of toxicity or overdose.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of Sublocade have not been evaluated. Its effect on sublingual buprenorphine has not been shown to be clinically significant but did result in longer half-lives and higher plasma levels in moderate to severe hepatic impairment. Patients known to have moderate to severe hepatic impairment are advised against starting Sublocade therapy due to the inability to rapidly adjust buprenorphine plasma levels. If a patient develops moderate to severe hepatic impairment while taking Sublocade, they should be monitored for signs and symptoms of buprenorphine toxicity or overdose and the depot should be excised if these occur within 2 weeks of Sublocade administration.

Renal Impairment

Clinical studies of Sublocade did not include adequate numbers of subjects with renal impairment to establish safety and efficacy. There were no differences observed in the pharmacokinetics of buprenorphine when 0.3 mg was administered intravenously to 9 dialysis-dependent and 6 normal patients.

Contraindications

- Hypersensitivity to buprenorphine
- Hypersensitivity to any component of the Atrigel® delivery system

Precautions

- **Boxed Warning:** There is significant risk of serious harm or death if Sublocade is injected intravenously due to its mechanism of solidifying into a mass upon contact with bodily fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, may result if administered intravenously. Do not administer intravenously, intramuscularly, or intradermally.
- Sublocade is only available through the Sublocade REMS Program due to the risk of serious harm or death mentioned above. Requirements of the REMS Program include:
 - Healthcare Settings and Pharmacies that order and dispense Sublocade must be certified in the Sublocade REMS Program.
 - Certified Healthcare Settings and Pharmacies must establish processes and procedures to verify Sublocade is provided directly to a healthcare provider for administration by a healthcare provider, and the drug is not dispensed to the patient.
 - Certified Healthcare Settings and Pharmacies must not distribute, transfer, loan, or sell Sublocade.
- Because Sublocade contains the Schedule III controlled substance buprenorphine, which may be abused similarly to other opioids, it is subject to criminal diversion and all patients receiving Sublocade should be monitored for progression of opioid use disorder and addictive behaviors.
- Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, postmarketing reports involved misuse by self-injection or concomitant use of benzodiazepines, other buprenorphine products, or other CNS depressants including alcohol. Warn patients of the danger of self-administering benzodiazepines or other CNS depressants while receiving Sublocade. Use caution when considering the use of Sublocade in patient with compromised respiratory function due to the risk of respiratory depression.
- Strongly consider prescription of naloxone for patients with opioid use disorder due to the risk of relapse and overdose. Educate patients on the signs of opioid overdose and inform them that naloxone may also be used for buprenorphine overdose.
- If patients are using other CNS depressant agents like alcohol, sedatives, opioid analgesics or illicit or prescribed benzodiazepines, additional monitoring may be required. Dose limitations for those using additional CNS depressants with buprenorphine are not recommended but if a patient is sedated at the time of intended buprenorphine dose administration, delay or omit the dose. Benzodiazepines are not first-line for anxiety or insomnia for patients taking buprenorphine and alternative treatments should be considered before co-prescribing benzodiazepines alongside buprenorphine.

- Injection site reactions may occur and commonly include pain, erythema, and pruritis. In some cases, severe reactions involving abscess, ulceration, and necrosis may occur. It may be necessary to surgically remove the depot, debride the area, administer antibiotics, and discontinue Sublocade. Inadvertent intramuscular or intradermal administration increases the risk of serious injection site reactions.
- Neonatal opioid withdrawal syndrome is expected with prolonged opioid use during pregnancy and pregnant women should be advised that it is life-threatening to the newborn but treatable. Management of opioid addiction should be discussed throughout the pregnancy and the risks and benefits of buprenorphine use weighed against the risk of relapsing illicit opioid use.
- Adrenal insufficiency has been reported with opioid use in some cases, typically associated with more than one month of use. Presentation of adrenal insufficiency may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, appropriate labs should be drawn and, if appropriate, replacement corticosteroid treatment should be administered. Patient should be slowly weaned off opioid. Other opioids may be tried because there are reports of this without recurrence of adrenal insufficiency, but none are identified as being more or less likely to cause recurrence.
- Abrupt discontinuation of Sublocade treatment may increase risk of opioid withdrawal, however this effect may be milder in comparison to withdrawal from full mu-opioid receptor agonists due to buprenorphine's effect as a partial mu-opioid receptor agonist. The long half-life of Sublocade results in a delay in withdrawal signs and symptoms to past the month following its discontinuation. The last dose administered before discontinuation correlates to the average length of time until withdrawal symptoms appear, with an average of 2 months after the 100 mg dose and 5 months after the 300 mg dose. Temporary transmucosal buprenorphine administration with tapering dosage may be useful for patients intending to discontinue Sublocade.
- Due to insufficient data, it is possible that buprenorphine may play a contributory or causative role in cases of cytolytic hepatitis and hepatitis with jaundice. Some cases were identified in which infection with hepatitis B or C, concomitant use of other potentially hepatotoxic drugs, or ongoing injecting drug use were identified as contributory or causative factors, but the data did not allow for exact etiology to be determined in all cases of hepatic events. Liver function tests are recommended prior to initiation of treatment to establish a baseline and monitoring of liver function is recommended each month, especially in those receiving the 300 mg dose. An etiological evaluation is recommended when a hepatic adverse event is suspected.
- Hypersensitivity to buprenorphine-containing products is possible and may result in bronchospasm, angioneurotic edema, and/or anaphylactic shock. Rashes, hives, and pruritis are the most common signs and symptoms, however.

- For patients currently physically dependent on a full mu-opioid receptor agonist like heroin, morphine, or methadone, non-equivalent doses of buprenorphine may result in withdrawal symptoms. Patients should be stabilized and tolerant of transmucosal buprenorphine before switching to injected Sublocade.
- If patients require acute pain management or anesthesia, a non-opioid analgesic is preferred when possible. If a high-affinity full opioid analgesic is required, it should be under the direct supervision of a physician with particular attention paid to respiratory function. If an opioid is required for anesthesia, the patient should be monitored by persons specially trained in the administration of anesthetic medications. Patients should instruct family members to inform healthcare provider that they are physically dependent on an opioid and using Sublocade in the event of an emergency.
- Sublocade is not appropriate for use in opioid naïve patients, as there have been reported death of opioid naïve individuals who received a 2 mg dose of buprenorphine as a sublingual tablet.
- Patients at risk for arrhythmia due to hypokalemia, hypomagnesemia, or clinically unstable cardiac disease (e.g. unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia) should be carefully evaluated before initiation of buprenorphine. In these cases, periodic electrocardiogram monitoring is recommended. Buprenorphine is recommended to be avoided in patients with either a history of Long QT Syndrome or a family member with the condition. Patients taking Class IA antiarrhythmic medications (e.g. quinidine, procainamide, or disopyramide) or Class III antiarrhythmic medications (e.g. sotalol, amiodarone, dofetilide) are also recommended to avoid buprenorphine use.
- Sublocade may impair mental or physical abilities required for performance of potentially dangerous tasks like operating a vehicle and patients should be cautioned that plasma levels are increasing for the first 2 months for those receiving the 100 mg dose and for the first 4 months for those receiving the 300 mg dose. Patients should be advised to exercise caution operating hazardous machinery during these times to establish certainty that Sublocade will not impair their ability to do so.
- Buprenorphine may produce orthostatic hypotension in ambulatory patients.
- Buprenorphine may elevate cerebrospinal fluid (CSF) pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.
- Buprenorphine may also cause an increase in the intracholedochal pressure, similar to other opioids and so should be administered with caution in patients with biliary tract dysfunction.
- Use of buprenorphine may cause difficulties in making diagnoses or treating patients with acute abdominal conditions.

- Children who are exposed to buprenorphine may experience severe and possibly fatal respiratory depression.

Adverse Effects

Non-injection site-related adverse reactions occurring in 2% or more of Sublocade® (buprenorphine) treated patients and at a rate greater than placebo after either two 300 mg doses followed by four 100 mg doses (A) or six 300 mg doses (B) were: (A/B)

- Constipation (25.1%/22.4%)
- Nausea (9.4%/8%)
- Vomiting (9.4%/5.5%)
- Fatigue (3.9%/6%)
- Headache (9.4%/8.5%)
- Sedation (3.4%/1.5%)
- Dizziness (2.5%/1)
- Somnolence (4.9%/2%)
- Increase in alanine aminotransferase (1%/5%)
- Increase in aspartate aminotransferase (3.4%/4.5%)
- Increase in blood creatine phosphokinase (5.4%/2.5%)
- Increase in gamma-glutamyl transferase (3%/4%)

Monitoring

Patients should be monitored for progression of opioid use disorder, addictive behaviors, and signs and symptoms of buprenorphine toxicity such as confusion, dizziness, miosis, hallucinations, hypotension, respiratory depression, seizures, or coma. Liver function tests are recommended prior to initiation of treatment to establish a baseline and monitoring of liver function is recommended each month, especially in those receiving the 300 mg dose.

Interactions

- Benzodiazepines and other central nervous system depressants (e.g. alcohol, sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, opioids):
- Concomitant use may result in additive pharmacologic effects such as respiratory depression. Cessation of other central nervous system depressants is recommended but decrease to lowest effective dose and close monitoring may be appropriate in some cases.
- CYP3A4 inhibitors (e.g. macrolide antibiotics, azole-antifungal agents, protease inhibitors): The effects of concomitant use with Sublocade have not been studied but the effects when taken with transmucosal buprenorphine are increased plasma concentration of buprenorphine and possibly increased or prolonged opioid effects. Plasma levels of buprenorphine should be monitored to check for adequacy if taken concomitantly. If patients that are already taking Sublocade require initiation of CYP3A4 inhibitor therapy, patients should

be monitored for signs and symptoms of overmedication. If toxicity is evident within 2 weeks of Sublocade administration, depot removal and subsequent switch to adjusted transmucosal buprenorphine dose may be necessary.

- CYP3A4 inducers (e.g. rifampin, carbamazepine, phenytoin, phenobarbital): The effects of concomitant use with Sublocade have not been studied but buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4, so potential interactions may occur when Sublocade is administered with agents that affect CYP3A4 activity. If the rate of buprenorphine metabolism is increased and the drug is cleared faster than intended, plasma concentrations may reach subtherapeutic levels with the approved dosing schedule.
- Antiretrovirals (non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g. efavirenz, nevirapine, etravirine, delavirdine)): NNRTIs are primarily metabolized by CYP3A4, an enzyme with high contribution to buprenorphine metabolism. If patients must take buprenorphine with an NNRTI, they should be monitored for increase or decrease in therapeutic effects of buprenorphine.
- Antiretrovirals (protease inhibitors (e.g. atazanavir, ritonavir)): Some protease inhibitors, such as the examples listed, show CYP3A4 inhibitory activity that resulted in increased levels of buprenorphine after sublingual administration. In postmarketing reports, patients have reported symptoms of opioid excess when receiving sublingual buprenorphine with atazanavir and with/(out) ritonavir.
- Serotonergic drugs (e.g. selective serotonin reuptake inhibitors, SNRIs, tricyclic antidepressants, mirtazapine, trazodone, tramadol, triptans, 5-HT₃ receptor antagonists, cyclobenzaprine, metaxalone): Concomitant administration of opioids with other serotonergic medications increases risk of serotonin syndrome and patients taking buprenorphine with one or more serotonergic agent should be monitored for symptoms of serotonin syndrome.
- Monoamine oxidase inhibitors (e.g. phenelzine, tranylcypromine, linezolid): MAOIs have been known to interact with buprenorphine and potentially produce the symptoms of serotonin syndrome or opioid toxicity. Patients who are taking an MAOI or who have discontinued one in 14 or less days are not recommended to initiate Sublocade therapy.
- Muscle relaxants: Buprenorphine may increase the incidence of respiratory depression in patients taking a muscle relaxant due to the enhancement of the neuromuscular blocking action of the latter. Patients receiving both buprenorphine and a muscle relaxant should be monitored for signs of respiratory depression.
- Diuretics: Opioids like buprenorphine may reduce the efficacy of diuretics by inducing the release of antidiuretic hormone and patients receiving both therapies concomitantly should be monitored for signs of decreased diuresis.
- Anticholinergic drugs: Anticholinergic medications may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Patients receiving both therapies should be monitored for signs of diminished diuresis or decreased gastric motility.

Risk Evaluation and Mitigation Strategy (REMS)

Sublocade REMS Program Requirements: Any pharmacy that dispenses Sublocade as well as any healthcare setting that purchases Sublocade from a distributor must be certified prior to dispensing/purchasing sublocade. Prescriber offices that only order Sublocade from a certified pharmacy for a specific patient are exempt from certification.

Drug Addiction Treatment Act (DATA)

Under the Drug Addiction Treatment Act, prescription use of this product in the treatment of opioid dependence is limited to healthcare providers who meet certain qualifying requirements. Providers must notify HHS of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

Efficacy

Multiple Dose Study of Opioid Effects by Injections of Buprenorphine in Participants with Opioid Disorder (NCT02044094) [2]

Thirty-nine participants were entered into this phase 2 placebo-controlled trial after determining that they were experiencing opioid withdrawal as defined by a Clinical Opiate Withdrawal Scale (COWS) score of greater than 12. All participants were then initiated on a daily dose of Suboxone sublingual film 8-24 mg at day -9.

A hydromorphone challenge was conducted on days -3 to -1 and the last day of Suboxone administration was day -1. Participants then received a dose of subcutaneously injected buprenorphine 300 mg and returned on days 4, 11, 18, and 25 for inpatient stays of 3 consecutive days. Randomized hydromorphone challenges were conducted during the inpatient stays as well as PK sample collection, Reinforcing Effects Tasks, and safety assessments. Participants received either 0 mg (placebo), 6 mg, or 18 mg of hydromorphone during the challenge. A Visual Analog Scale (VAS) measuring "drug-liking" was used to measure the response to the hydromorphone challenge and was scored from 0 to 100.

The effect of Sublocade in reducing hydromorphone drug-liking in 6 and 18 mg challenges was not inferior to the effect in challenges with placebo. A difference of score between the placebo and hydromorphone challenges on the VAS of less than 20 was considered to indicate near-complete blockade by Sublocade. All 12 weeks of treatment showed blockade for 6 and 18 mg but considerable variation is notable among individuals' scores over time. Sublocade showed full blockade throughout 8 weeks following 2nd injection, whereas sublingual buprenorphine was shown to not provide full blockade with 18 mg dose of hydromorphone.

Treatment-Seeking Participants with Opioid Use Disorders Assessing Tolerability of Depot Injections of Buprenorphine (NCT02357901) [3]

In this phase 3, double-blind, placebo-controlled trial, after a 2-week screening period, participants who were treatment-seeking and met DSM-5 criteria for moderate or severe opioid use disorder began a 3-day open-label run-in induction phase with Suboxone sublingual buprenorphine film, followed by a dose adjustment period for 4 to 11 days to reach a daily Suboxone dose between 8 and 24 mg. The study was conducted over 24 weeks. After randomization, patients received either Sublocade 300 mg or placebo on days 1 and 29. Afterwards, they received 4 injections of either Sublocade 100 mg, Sublocade 300 mg, or placebo. Patients were randomized in 4:4:1:1 proportion with 203 in the 300/100 mg group, 201 in the 300/300 mg group, and two groups of 50 in the placebo group.

504 patients underwent weekly urine drug screens and self-reported use of illicit opioid use during the study but were given a grace period from week 1 to week 4 to allow for stabilization on treatment. Opioid use detected during this period was not included in analysis. Missing urine drug screen samples or self-reports during the period after week 4 were considered as positive for illicit opioids.

During the treatment period after week 4, Sublocade was superior to the placebo group with statistical significance. The proportion of patients achieving treatment success (\geq to 80% opioid-free weeks) was statistically significantly higher in both Sublocade treatment groups than in the placebo group (28.4% [300 mg/100 mg], 29.1% [300 mg/300mg], 2% [placebo]).

Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine with Naloxone for Treatment of Opioid Use Disorder. [4]

Effectiveness of Sublocade has been established in a randomized, double-blind, double-dummy trial in treatment-seeking patient with moderate-to-severe opioid use disorder. Participants were randomized to receive either daily sublingual placebo as well as weekly & then monthly subcutaneous buprenorphine (SC-BPN group), or daily sublingual buprenorphine with naloxone with matched weekly & then monthly subcutaneous placebo injections (SL-BPN/NX group).

The aim of the study was to establish noninferiority of subcutaneous buprenorphine in comparison to sublingual buprenorphine in treating opioid use disorder. The primary endpoints for the study were the response rate and the mean proportion of opioid-negative urine samples for 24 weeks. Response to treatment was defined as having no evidence of illicit opioid use for at least 8 of 10 prespecified points during weeks 9 to 24 of the trial, with 2 points occurring at week 12 and during weeks 21-24. Eligible participants for the study were between the ages of 18 and 65.

Participants were excluded if they were already receiving pharmacotherapy for opioid use disorder within 60 days of the trial, if they were pregnant, nursing, or planning to become pregnant, were hypersensitive to buprenorphine or the excipients in the

subcutaneous injection, were using strong cytochrome P450 3A4 inhibitors, had recent suicidal ideation, had risk for torsade de pointes, had QTc prolongation of >450 ms in men and >470 ms in women, had AST or ALT levels more than 3 times the reference range maximum, had bilirubin or creatinine levels 1.5 times the reference range maximum, or had pending legal action.

Of the 428 participants randomized and placed into 2 groups (213 in SC-BPN group & 215 in SL-BPN/NX group), the percent of responders in the SC-BPN group (17.4%) was greater than that of the SL-BPN/NX group (14.4%). This statistically insignificant difference between the groups' response rates indicated non-inferiority between sublingual and subcutaneous buprenorphine therapy. Additionally, the SC-BPN group produced a higher average percentage of weekly opioid-negative urine samples during the 24-week period (34.2%) compared to the SL-BPN/NX group (27.4%).

Summary of Notable Treatment Guidelines for Initial Management of Opioid Use Disorder:

College of Psychiatric and Neurologic Pharmacists (CPNP) Pharmacist Toolkit: Medication Management of Opioid Use Disorder [5]

- Approved treatments for opioid use disorder treatment include buprenorphine/naloxone, methadone, and naltrexone.
- Subcutaneous buprenorphine is recommended to be administered as 300 mg injected into the abdomen once monthly for 2 months, then 100 mg once monthly with the option to increase dose back to 300 mg per month if inadequate response with 100 mg per month.

American Society of Addiction Medicine National Practice Guideline for the Treatment of Opioid Use Disorder [6]

- Recommendation for using buprenorphine for patients with opioid use disorder, who are able to give informed consent and have no specific contraindications to treatment.
- Only a single prior dose of transmucosal buprenorphine is required prior to initiation of subcutaneously injected buprenorphine.

Department of Veterans Affairs and Department of Defense Clinical Practice Guideline for the Management of Substance Use Disorders [7]

- Strong recommendation for use of Buprenorphine/naloxone in any setting; or methadone or buprenorphine/naloxone provided through an accredited Opioid Treatment Program. Recommendations were broadly for buprenorphine and did not specify recommendation for subcutaneously administered buprenorphine.

Patient Preference [8]

One study found that a majority of people who used opioids in the polled sample were willing to receive prescribed buprenorphine in the future, and were receptive to

receiving either oral, injectable, or implantable options. 54.7% of respondents (185 of 338 total) responded that they were willing to receive some sort of buprenorphine treatment, however, those that responded “no” to the question of whether they would “be willing to be prescribed buprenorphine or Suboxone in the future” were not asked about any of the newer buprenorphine formulations such as the subcutaneous injection. Of those who responded that they would be interested in being prescribed buprenorphine 23.1% (40 individuals) stated that they preferred an injection over a sublingual or implant formulation.

Dosage Forms/Cost

Each injection of Sublocade delivers either 100 or 300 mg of buprenorphine in either 0.5 mL or 1.5 mL, respectively.

A single carton containing one prefilled syringe of either available strength costs \$1829.05 each.

Special Considerations

Any pharmacy that dispenses Sublocade as well as any healthcare setting that purchases Sublocade from a distributor must be certified in the REMS program prior to dispensing/purchasing sublocade. Prescribers must meet the requirements of the Drug Addiction Treatment Act (DATA).

Summary/Conclusion

Sublocade® (buprenorphine extended-release) injection, for subcutaneous use is FDA approved for opioid use disorder and is supported by clinical evidence and treatment guidelines. The other buprenorphine formulary products are buprenorphine sublingual tablets and buprenorphine-naloxone sublingual film and sublingual tablets. Other formulary medications approved for opioid use disorders also include methadone and naltrexone microspheres (Vivitrol®). All of these treatments are listed as reserve use drugs with guidelines for use. The Sublocade once-monthly option may provide a more desirable dosing schedule and consistency of drug concentration in plasma but its cost and lack of significant benefit over sublingual buprenorphine makes it undesirable as a formulary addition for inpatient facilities.

Recommendation

Addition of Sublocade® (buprenorphine extended-release) injection, for subcutaneous use to the formulary is not recommended at this time.

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