HHSC Psychiatric Executive Formulary Committee Minutes

Date

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on April 5, 2019 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Messer, Chair at 9:35 a.m.

Members			
Jean Baemayr, PharmD- Secretary	√	Ashton Wickramasinghe, MD	√
John Bennett, M.D.	√	Vacant- local authority practitioner	
Bonnie Burroughs, PharmD	√	Vacant- local authority practitioner	
Barbara Carroll, RN	√	Tim Bray (non-voting)	Absent
Cleveland "Chip" Dunlap, RN	Absent	Connie Horton, RNP (non-voting)	Absent
Catherine Hall, PharmD	√	Raul Luna, RN, MSN (non-voting)	Absent
Jeanna Heidel, PharmD	√	Mike Maples (non-voting)	Absent
Jeff Matthews, MD	√	Nina Muse, M.D. (non-voting)	√(partial)
Mark Messer, DO- Chair	√	Peggy Perry (non-voting)	Absent
David Moron, MD	√	Rachel Samsel, (non-voting)	Absent
Scott Murry, MD	√	E. Ross Taylor, MD (non-voting)	√
Kenda Pittman, PharmD	Absent		
Rishi Sawhney, MD	√		
Glenn Shipley, DO	√		

Guests Present: Ann Richards, PharmD, State Hospital System; Rania Kattura, PharmD, Clinical Pharmacist Austin State Hospital; Brittany Parmentier, PharmD, Clinical Assistant Professor, UT Tyler; Alisha Donat, PharmD, Pharmacy Resident, Brad Fitzwater, MD

Introduction and Other Information

Dr. Messer welcomed the committee members.

Dr. Kubista has resigned from the committee. Dr. Moron, Medical Director of Rio Grande State Center, was introduced as a new member.

Approval of Minutes of January 11, 2019

On a motion of Dr. Heidel, seconded by Dr. Matthews, the minutes of the January 11, 2019 meeting were approved as previously distributed.

Formulary Name Change
Tim Bray has assigned a new name to the committee: "The HHSC Psychiatric Executive Formulary Committee." The formulary will now be known as "The HHSC Psychiatric Drug Formulary."

Old Business

Conflict of Interest
The PEFC Conflict of Interest Policy was distributed to the committee members prior to the January meeting. Voting committee members are required to submit annual disclosures.

The following member's disclosure statements were received after the January meeting:

Jeanna Heidel

Jeffery Matthews

Ashton Wickramasinghe

David Moron

The 2019 annual disclosures have now been received from all voting members. No members indicated the presence of any conflicts of interest.

Psychotropic Medication Utilization Parameters for Children & Youth (April 2018)
The *Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health* was distributed to the systems academic partners (University of Texas, Texas A&M, and Texas Tech facilities) for review on March 4, 2019, with an April 5, 2019 due date to return any comments. All comments received will be forwarded back to the Psychotropic Medication Utilization Parameters for Children & Youth workgroup. The final draft document will be presented to the PEFC for approval at a later date.

TAC Title 25, Part 1, Chapter 415, Subchapter C (April 2017)
The required Rulemaking Notification Form (RNF) has been submitted to the Rules coordination Office. A new PEFC workgroup will be formed once approval to move forward has been received. The workgroup will be comprised of committee members representing state hospitals, state supported living centers, and community mental health centers.

Psychotropic Audit Criteria & Guidelines Review-Antidepressants (April 2012)
Audit criteria and guideline reviews for amoxapine, mirtazapine, venlafaxine, SSRI's (paroxetine, fluvoxamine), MAOI's, and TCA's are pended until the next PEFC meeting.

New Business

Adverse Drug Reaction Reports

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

1. ADR: NMS in a 24-year-old male admitted to an inpatient psychiatric hospital from jail with a diagnosis of schizophrenia, substance use disorder (marijuana, inhalant use and psilocybin) and possible previous traumatic brain injury. While incarcerated, he was prescribed quetiapine 100 mg at bedtime for approximately 3 months prior to admission; however, he denies taking this medication. He is reported to be a poor historian and denies prior psychiatric hospitalization although endorses past prescriptions for quetiapine, aripiprazole, alprazolam, and clonazepam.

   On admission, labs were normal except for mildly elevated CO2 at 33 mmol/L. He was agitated, yelling, intrusive, disorganized and disheveled. He received STAT doses of haloperidol 10 mg orally on days 0, 4, 5 and 6 and 5 mg orally on day 7; olanzapine ODT 10 mg was administered on day 2 and twice on day 3. On day 6 court ordered medication administration was granted and haloperidol 10 mg po daily (with IM injection as backup) was prescribed. The following day, the dose was increased to haloperidol 5 mg in the morning and 10 mg at night with benztropine 0.5 mg twice daily for "EPS prevention." He had a visitor on day 18 and it was discovered days later that the visitor had given the patient an unknown amount of memantine. The patient had an episode of emesis after this visit and at 01:05 am. He began yelling loudly in a bizarre way and later laid on the floor for a few minutes in a stupor with pupils dilated, but then was able to follow verbal directions. Vital signs were stable and he was administered haloperidol 10 mg, diphenhydramine 50 mg, and lorazepam 2 mg STAT orally.

   Later that night he refused his oral haloperidol dose so Haloperidol 10 mg IM backup was administered along with STAT lorazepam 2 mg IM. After the injections, he appeared restless, confused, poorly oriented and unaware of his surroundings. He was sent to a local medical hospital to rule out a cause for the sudden change in mental status. At the medical hospital, he was combative and attempted to remove his IV several times. Toxicology and head CT were negative and labs aside from a CK of 489 U/L (normal range 22 - 198 U/L) were normal. Vitals were reported to be normal except for pulse, which was elevated at 112 bpm. He was treated with lorazepam for agitation and given fluids. He was discharged the following day. Upon arrival to the psychiatric hospital at 05:14 am, he was noted to be in a disoriented, disorganized state with unsteady gait that required wheelchair use from the transporting van. He was assessed upon return and was able to move all extremities but would not relax his arms to allow full assessment. Possible rigidity of left arm was noted. He had a pulse

of 107 bpm and elevated temperature of 99.9° for which he received acetaminophen 650 mg. He would try to get out of the wheelchair and nearly fell multiple times. The patient became increasingly agitated, combative, disorganized and confused with diaphoresis and temperature of 100.9°. He was again sent to the medical hospital at 4:15 pm that same day. This time he was admitted to the ICU, diagnosed with NMS and treated with fluids, lorazepam, and acetaminophen. His temperatures remained elevated for the next 2 days. The CPK was 766 U/L the day of admission and decreased to 449 U/L the following day. He was discharged 3 days later off haloperidol and prescribed lorazepam 1 mg po three times daily and 1 mg po as needed for agitation, rigidity, and elevated temperature.

2. ADR: Seizure event followed by severe neutropenia in a 42-year-old Hispanic male admitted to the psychiatric hospital approximately 3.5 years prior to the event. Diagnoses include Schizophrenia, Major Neurocognitive Disorder and Hyperlipidemia Although he did not have a diagnosis of seizure disorder per his admission history, he did have an EEG in September of 2018 that showed spike activity and he does have risk factors for seizures including a history of TBI and CNS abnormalities per past MRI. Over the past 2.5 years, he has been prescribed various maintenance doses of clozapine ranging from 250 mg to 400 mg daily. Two months prior to the seizure event, his clozapine dose had been reduced from 300 mg daily to 250 mg daily. Divalproex was tapered and discontinued 3 months prior to the seizure event. This was followed by a brief period of treatment with topiramate followed by lamotrigine initiation one month prior to the seizure. In addition to clozapine 250 mg at bedtime, simvastatin 20 mg daily, lamotrigine 50 mg twice daily, glycopyrrolate 0.5 mg twice daily and donepezil 10 mg at bedtime were also prescribed. Donepezil 5 mg daily had been recently started and titrated to a dose of 10 mg daily 2 months prior to the seizure event. The seizure lasted approximately 5 minutes and was noted to be grand mal with upper and lower extremity rigidity that resulted in a fall where the patient hit the back of his head. He was transferred to a local medical hospital for treatment. After the seizure, donepezil and clozapine were both continued at previously prescribed doses. A clozapine level 3 days after the event was 961 ng/mL. The last three monthly ANCs were wnl at 3.5, 3.2 and 2.8 K/mm^3. Levetiracetam 500 mg twice daily was added to the medication regimen. Lamotrigine was titrated up to a dose of 100 mg twice daily along with the addition of memantine 5 mg twice daily. An ANC 2 weeks after the seizure indicated moderate neutropenia with an ANC of 1.0 K/mm^3. A subsequent ANC the following day was 0.7 K/mm^3. Both memantine and clozapine were discontinued and olanzapine 10 mg was prescribed. The following day, the ANC declined further at 0.5 K/mm^3. Olanzapine and lamotrigine were discontinued and oxcarbazepine 150 mg twice daily and clonazepam 1 mg at bedtime were prescribed. The next two days, the ANC declined further at a nadir of 0.3 K/mm^3 (severe neutropenia). Oxcarbazepine was discontinued. The following day the

ANC increased slightly to 0.4 K/mm^3 and two days after that was almost back to baseline at 2.4 K/mm^3.

The two medications prescribed prior to the seizure event which are most likely to lower seizure threshold are clozapine (9%) and donepezil (8.4%) per the World Health Organization article on seizure risk with neuroactive drugs database publication [Seizure 2010;19:69-73]. He has been on clozapine for quite some time and the 300 mg per day dose was decreased to 250 mg per day. Donepezil was more recently initiated and increased to 10 mg. Although clozapine is well known to contribute to drug-induced seizures, it may have been the addition of donepezil along with additional risk factors for seizure that contributed. Although clozapine is most commonly associated with neutropenia, it is possible the addition and titration of lamotrigine may have contributed the development of severe neutropenia that rebounded 5 days after drug discontinuation to close to baseline ANC levels. The brief initiation of oxcarbazepine and possibly olanzapine could have delayed the time to rebound as these medications have also been reported to possibly contribute to neutropenia. Two case reports were found that also report development of agranulocytosis after addition of lamotrigine to clozapine treatment [Psychiatria Danubina 2015;27(suppl 1):459-461 and J Clin Psychopharmaol 2011;31(5):665-667]. One of the cases occurred several years after being prescribed clozapine at a stable dose and a dose increase of lamotrigine from 150 mg per day to 250 mg per day. A kinetic or protein binding interaction is not known. There is one case report that does describe an increase in clozapine level after introduction of lamotrigine [Am J Psychiatry 201;158(11):1930].

3. ADR: Myocarditis in a 25 yo HM who had been diagnosed with schizophrenia, cannabis dependence, and obesity. He has failed multiple antipsychotics, most recently the combination of olanzapine and lurasidone. His only other medication at the time was omeprazole 40 mg qd. He had been on bupropion, buspirone, propranolol, and melatonin but these were discontinued because he consistently refused them. On 1/3/19, clozapine was started with the following titration schedule: 1/3/19 = 12.5 mg daily-hs. 1/4/10 = 12.5 mg BID. 1/5/19-1/6/19 = 25 mg BID. 1/7/19-1/8/19 = 50 mg BID. 1/9/19-1/11/19 = 75 mg BID. 1/12/19-1/14/19 = 100 mg BID. 1/15/19-1/18/19 = 125 mg BID. 1/18/19-1/20/19 = 100 mg BID. Baseline and weekly (x4) troponin, CRPs were ordered. On 12/28/18, troponin = < 0.010 (< 0.010), CRP = 0.3 mg/dl (< 0.5). On 1/15/19 troponin T = < 0.010, CRP = 1.7 mg/dl (< 0.5).

   On 1/18/19, his pulse = 135 bpm, recheck of 140 bpm. Clozapine was decreased from 125 mg bid to 100 mg bid, atropine drops were discontinued, and propranolol 10 mg bid was started.

   On 1/19/19, he complained of 7/10 chest pain. No SOB or diaphoresis. EKG performed and he received acetaminophen 975 mg and Mylanta® 30 ml.

On 1/20/19, he continued to complain of 10/10 sharp chest pain and feeling "woozy". At 0721, bp = 138/98 mmHg, p = 105 bpm, temp = 98.0°, r = 20 breaths/min, O2 sats = 98%. Another EKG performed and stat troponin, CPK, CBC were ordered. EKG showed ST changes. Omeprazole was increased to 40 mg bid and received Mylanta® 30 ml. Stat troponin came back at 1.76 (< 0.010) and he was transported to the community hospital. At 0910, bp = 137/93 mmHg, p = 113 bpm, temp = 97.9°, r = 16 breaths/min, O2 sat = 99%. He received aspirin 325 mg and clozapine 100 mg bid was discontinued.

On 1/22/19, he returned from the community hospital, where he had been diagnosed with myocarditis on 1/20/19. Cardiology appointment was scheduled for early February. CRP, BNP, EKG, troponin, and CXR were ordered. He was started on colchicine 0.3 mg bid x 30 days, and ibuprofen 400 mg q 8 h x 30 days. Also on omeprazole 20 mg bid, propranolol 10 mg bid, Zofran 4 mg q 8 h prn n/v. Pulse was still 110 bpm.

On 1/24/19, he continued to complain of mild CP, mild SOB. BP = 125/78 mmHg, p = 105 bpm. Propranolol was increased to 10 mg TID. On 1/24/19, CRP = 0.6 mg/dl (< 0.5 mg/dl). All since have been < 0.1 mg/dL. On 1/24/19, troponin = < 0.010 and it has remained at this level. On 1/24/19, nt-probnp = < 50 pg/ml (per lab, if nt-probnp < 300 pgml, heart failure is unlikely for all ages.) On 1/30/19, nt-probnp = 131 pg/ml but all others have been < 50 pg/ml. On 2/13/19, the cardiologist recommended stopping ibuprofen and continuing colchicine 0.3 mg bid for a total of three months. His psychosis is currently being treated with aripiprazole.

New Drug Applications

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

1. Losartan (Cozaar®)

Pended until next meeting. Dr. Parmentier will prepare the monograph and include a comparison of available angiotensin II receptor blockers (ARBs).

2. Naloxone nasal spray -presented by Dr. Kattura

Please refer to Appendix A for the monograph and application that were considered when determining action by the committee.

On a motion of Dr. Matthews, seconded by Dr. Messer, it was recommended to add naloxone nasal spray to the formulary as a reserve agent to be dispensed only as a discharge medication for patients that have been determined to be at risk of an opiate overdose. The formulary check list was completed and no issues were detected.

3. Risperidone SubQ (Perseris®)- presented by Dr. Kattura

Please refer to Appendix B for the monograph and application that were considered when determining action by the committee.

The committee discussed cost, dosing, and administration of Perseris®. Currently, available strengths correspond to either 3 or 4 mg of oral risperidone, which is less than the typical dose needed for stabilization of state hospital patients. Preparing the dose for administration requires that the product remain at room temperature for at least 15 minutes. Mixing involves 5 cycles of a gentle a back-and-forth transfer between a syringe containing the risperidone powder and a syringe containing the delivery liquid, followed by an additional 55 cycles of vigorous mixing. Subcutaneous administration into the abdomen with the supplied 18-gauge 5/8" needle may result in a lump that may take several weeks to resolve and should not be rubbed or massaged by the patient, or covered with a belt or waistband.

On a motion of Dr. Messer, seconded by Dr. Hall, the committee declined to add risperidone SubQ (Perseris®) to the formulary.

4. Aripiprazole lauroxil (Aristada Initio®)- presented by Dr. Parmentier

Please refer to Appendix C for the monograph and application that were considered when determining action by the committee.

On a motion of Dr. Matthews, seconded by Dr. Messer, it was recommended to add aripiprazole lauroxil (Aristada Initio®) to the formulary as a reserve agent requiring that the patient has demonstrated tolerability to aripiprazole through either a two-week trial of oral aripiprazole or a history of aripiprazole LAI use. The formulary check list was completed and no issues were detected. As this is a new product on the market, system Aristada Initio use will be evaluated in one year to determine if any adverse drug reactions or medication errors have occurred.

5. Esketamine nasal spray (Spravato®)- presented by Dr. Hall

Please refer to Appendix D for the monograph and application that were considered when determining action by the committee.

On a motion of Dr. Heidel, seconded by Dr. Messer, it was recommended to add esketamine nasal spray (Spravato®) to the formulary as a reserve agent with the following restrictions: All REMS requirements must be followed. The patient must have a history of three failed antidepressant trials of adequate dose and duration involving more than one class of antidepressant. The patient's blood pressure must be monitored for two hours post administration. The patient should have a depressive episode rating of severe as measured using the Montgomery-Asberg Depression Rating Scale (MADRS). The severity of the depression should be measured using the MADRS at baseline and then weekly for the duration of treatment with esketamine nasal spray. The formulary check list was completed and no issues were detected. As this is a new product on the market, system

esketamine use will be evaluated in one year to determine if any adverse drug reactions or medication errors have occurred.

Psychotropic Audit Criteria and Guidelines Review Schedule

The committee reviewed the proposed schedule for review of the audit criteria and guidelines for the use of psychotropic medications.

On a motion of Dr. Heidel, seconded by Dr. Matthews, the review schedule was approved. Dr. Richards will form a workgroup that will include a clinical pharmacist and a psychiatrist. Dr. Messer, Dr. Hall, and Dr. Parmentier have volunteered to be a part of the workgroup.

Naltrexone, Topiramate Audit Criteria and Guidelines

The committee reviewed the PEFC website placement of the naltrexone and topiramate audit criteria and guidelines and audit checklist documents. Documents for both drugs are currently posted in the Chemical Dependency Adjunct group as well as being posted under their respective drug name. The committee approved the retirement of the documents posted individually, keeping the versions posted in the chemical dependency adjunct group. The indications for use on the naltrexone audit criteria and guidelines and audit checklist posted in the chemical dependency adjunct will be updated to add self-injurious behavior.

On a motion of Dr. Matthews, seconded by Dr. Messer, the above changes were approved.

The committee also discussed what information from the criteria and guidelines should be included on the audit sheets and determined that only three items: indications, contraindications, and monitoring parameters would be included on audit checklists.

On a motion of Dr. Heidel, seconded by Dr. Messer, the above clarification to the audit checklists was approved. The current checklists will be updated as they are reviewed per the psychotropic monitoring audit criteria and guidelines review schedule.

Psychotropic Monitoring Inpatient Guidelines

The committee reviewed an updated Psychotropic Monitoring Inpatient Guidelines quick reference document. This document is based on the current psychotropic audit criteria and guidelines. The committee recommended adding "(clozapine)" after *BNP every 3 months or as clinically indicated* under ongoing monitoring for Atypical Antipsychotics and clarifying the listing of drugs that only require pregnancy testing or pregnancy testing with monitoring for suicidal ideations.

On a motion of Dr. Moron, seconded by Dr. Matthews, the updated document was approved for posting to the PEFC website.

Pregnancy Testing Requirements
The committee reviewed the various ways that pregnancy testing requirements are described in the psychotropic monitoring audit criteria and guidelines. "Baseline and as clinically indicated" was recommended to be the standard phrasing.

On a motion of Dr. Messer, seconded by Dr. Matthews, the current checklists will be updated as they are reviewed per the psychotropic monitoring audit criteria and guidelines review schedule.

Cytochrome P450 Chart Review
The committee reviewed the updated chart in two different layouts- legal and letter. The committee approved the letter format for posting to the PEFC website.

On a motion of Dr. Bennett, seconded by Dr. Messer, the updated chart was approved for posting to the PEFC website.

Fluphenazine Decanoate – Haloperidol Decanoate Conversion Table
The committee reviewed the table, which describes dosing strategies for switching between fluphenazine decanoate and haloperidol decanoate in the event that a scheduled dose of either medication is unavailable due to a drug shortage.

On a motion of Dr. Bennett, seconded by Dr. Heidel, the conversion table was approved to be posted to the PEFC website.

Hepatitis C Drug Purchases
For the second quarter of fiscal year 2019 (December 2018-February 2019), the following purchases for drugs to treat hepatitis C were made:

State Hospitals: $43,163.08

State Supported Living Centers: none

GLP-1 Agonist Review (April 2018)
At the April 2018 meeting, a 12-month review of drug purchases was completed for the GLP-1 agonists. At that time, it was recommended to review the purchases again in one year to determine if a GLP-1 agonist should be considered for addition to the formulary. The GLP-1 agonist purchases are:

Facilities	3/1/16 to 2/28/17	3/1/17 to 2/28/18	3/1/18 to 2/28/19
State Hospitals	$4,372.20	$5,654.24	$11,564.10
State Supported Living Centers	$42,125.12	$38,432.46	$95,571.03

Liraglutide (Victoza®) accounted for all of the State Hospital purchases. Dulaglutide (Trulicity®) was the agent purchased by the SSLCs in the highest quantity and dollar volume for the last 12 months, followed by liraglutide. After reviewing the

purchase history, the committee recommended evaluating a GLP-1 agonist for addition to the formulary. Dr. Hall will present a comparison of available products at the next PEFC meeting.

Quarterly Non-Formulary Drug Justification Report

For the first and second quarters of fiscal year 2019, only the State Hospitals reported use of non-formulary agents. TCID has been removed, as they are not a part of the HHSC Health and Specialty Care System. The SSLC facilities currently do not have the reporting capabilities to obtain the non-formulary drugs from their computer system but are working with the vendor to create a report. The following were the top non-formulary agents, by number of orders, that were prescribed in the State Hospitals:

losartan (Cozaar®)
clotrimazole/betamethasone cream (Lotrisone®)
solifenacin (Vesicare®)
apixaban (Eliquis®)

Drug Deletions

The committee reviewed the Reserve Drug list and considered the following:

a) Removing medications specific to the Texas Center for Infectious Disease (TCID), as TCID is under DSHS while the state hospitals and state supported living centers are not. The following drugs were reviewed:

Cycloserine- remove from formulary

epoetin- remove TCID reference in Reserve Table, but keep on formulary

linezolid- remove reference to TCID. Add "When recommended by a consultant physician."

b) fentanyl lozenge- remove from formulary

c) ketamine nasal spray- remove from formulary as a commercially approved product approved by the FDA is now available.

On a motion of Dr. Matthews, seconded by Dr. Messer, these changes to the formulary were approved.

New Dosage Strengths

The committee did not consider adding any additional products not already specified in the sectional review or new drug application review.

Drug Formulary Sectional Review:

In reviewing the formulary drug listings for respiratory agents, antihistamines, and antiemetics/antivertigo agents, Dr. Hall made the following recommendations:

1. Respiratory Agents

a) Short acting
    - delete albuterol syrup
    - delete albuterol extended release tablets
b) Miscellaneous Respiratory Drugs
    - delete cromolyn nebulization and nasal solutions
    - delete zafirlukast tablet
c) Add designated abbreviations
    - Short Acting $Beta_2$ Agonist (SABA)
    - Long Acting $Beta_2$ Agonist (LABA)
    - Short Acting Anticholinergic (SAMA)
    - Long Acting Anticholinergic (LAMA)Combination Short Acting $Beta_2$ Agonist plus Anticholinergic (SABA/SAMA)
    - Combination Long Acting $Beta_2$ Agonist plus Corticosteroid (LABA/ICS)
    - Inhaled Corticosteroid (ICS)

2. Antihistamine, Cough, and Decongestant Preparations
    - Delete brompheniramine-pseudoephedrine tablets
    - Delete hydrocodone-guaifenesin liquid

On a motion of Dr. Hall, seconded by Dr. Heidel, the changes recommended above were approved and the formulary will be updated.

Issues from the Medical Director, State Hospital System

Dr. Muse was not present at this point of the meeting and did not provide any information to report.

Issues from the Medical Director, State Supported Living Centers

Dr. Taylor and Dr. Shipley had no issues to report to the committee.

FDA Drug Recalls and Safety Communications

The FDA has issued the following recall communications that may impact our facilities:

Irbesartan (Avapro®)

Prinston Pharmaceutical Inc., dba Solco Healthcare LLC., has initiated a voluntary recall of one (1) lot of irbesartan and seven (7) lots of irbesartan HCTZ Tablets to the consumer level due to the detection of trace amount of an unexpected impurity N-nitrosodiethylamine (NDEA) found in an active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceuticals. NDEA is a substance that occurs naturally in certain foods, drinking water, air pollution, and industrial processes, and has been classified as a probable human carcinogen as per International Agency for Research on Cancer (IARC) classification.

Losartan (Cozaar®)

Torrent Pharmaceuticals Limited is expanding its voluntary recall from 10 lots of Losartan potassium tablets USP to include 6 lots of Losartan potassium and hydrochlorothiazide tablets, USP, to the consumer level due to the detection of trace amounts of NDEA found in an API manufactured by Hetero Labs Limited. Torrent is only recalling lots of losartan containing products that contain NDEA above the acceptable daily intake levels released by the FDA. To date, Torrent Pharmaceuticals Limited has not received any reports of adverse events related to this recall.

Torrent Pharmaceuticals Limited is voluntarily recalling 60 lots of Losartan potassium tablets USP and 54 lots of Losartan potassium/ hydrochlorothiazide tablets, USP, to the consumer level due to the detection of trace amounts of N-Methylnitrosobutyric acid (NMBA) a possible process impurity or contaminant in found in an API manufactured by Hetero Labs Limited. Torrent is only recalling lots of losartan-containing products that contain NMBA above the acceptable daily intake levels released by the FDA. To date, Torrent Pharmaceuticals Limited has not received any reports of adverse events related to this recall.

Legacy Pharmaceutical Packaging, LLC is recalling 40 repackaged lots of Losartan Tablets USP to the consumer level. This recall was prompted due to Camber Pharmaceuticals, Inc. issuing a Voluntary Nationwide Recall of Losartan Tablets, USP, due to the detection of trace amounts of NMBA in an API manufactured by Hetero Labs Limited.

Camber Pharmaceuticals, Inc. is recalling 87 lots of Losartan Tablets USP 25 mg, 50 mg, and 100 mg to consumer level. This recall was prompted due to the detection of trace amounts of N-NMBA in an API manufactured by Hetero Labs Limited.

Macleods Pharmaceuticals Limited is voluntarily recalling one lot of Losartan Potassium/Hydrochlorothiazide combination tablets 100mg/25mg to the consumer level due to the detection of trace amounts of NDEA found in finished product manufactured with API made by Hetero Labs Limited.

Valsartan (Diovan®)

AurobindoPharma USA, Inc. and Acetris Health LLC. are conducting a voluntary recall expansion of 39 lots of Valsartan and Amlodipine and Valsartan tablets to the consumer level due to the detection of trace amounts of NDEA found in the finished drug product. This recall is an expansion of the recall initiated 12/31/18. The expansion relates to lots distributed under the labels for AurobindoPharma USA, Inc. and Acetris Health, LLC. To date, AurobindoPharma USA, Inc. has not received any reports of adverse events related to this recall.

The FDA has issued the following safety communication that may affect our facilities:

Loperamide (Imodium A-D®)

Warnings (additions underlined)

Ask a doctor before use if you have

- Fever
- mucus in the stool
- a history of liver disease
- a history of abnormal heart rhythm

Risperidone (Risperdal®)

Adverse Reactions 6.2 Postmarketing Experience *(Additions and/or revisions are underlined)*

These adverse reactions include: alopecia, anaphylactic reaction, angioedema, atrial fibrillation, cardiopulmonary arrest, diabetic ketoacidosis in patients with impaired glucose metabolism, dysgeusia, hypoglycemia, hypothermia, ileus, inappropriate antidiuretic hormone secretion, intestinal obstruction, jaundice, mania, pancreatitis, pituitary adenoma, precocious puberty, pulmonary embolism, QT prolongation, **somnambulism**, sudden death, thrombocytopenia, thrombotic thrombocytopenic purpura, urinary retention, and water intoxication.

News Briefs

The following information was shared with the committee members:

FDA Approves Expanded Use Of Tdap Vaccine For Repeat Vaccination.

NJBIZ (NJ) (1/15, Vecchione) reports the Food and Drug Administration "approved the expanded use of [Sanofi's] Adacel (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine Adsorbed) to include repeat vaccination to help protect against tetanus, diphtheria and pertussis." Sanofi provided results of a study on the effectiveness of the vaccine for repeat vaccinations in adults "to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices for their consideration in future recommendations."

FDA Says Impurities In Recalled Blood Pressure Drugs Were Caused By Change In Manufacturing Process

The Washington Post (1/25, Johnson) reported the Food and Drug Administration said that the impurities found in many generic blood pressure drugs over the past several months are a byproduct of the manufacturing process for the drugs' active ingredients, which was changed several years ago. Reuters (1/25, Erman) reported the agency said that the impurities may occur "when specific chemicals and reaction conditions are present in the manufacturing process" and "may also result from the reuse of materials, such as solvents." The Wall Street Journal (1/25, Burton, Subscription Publication) reported the Food and Drug Administration said that two million people may have been exposed to blood pressure drugs

manufactured in China and India that were contaminated with the impurities. The agency said that at least half of those patients are in the US.

Loperamide Overdoses Mostly Due To Abuse, Study Suggests.

Healio Gastroenterology (2/4, Young) reports on a study published in Clinical Toxicology finding that "most patients who overdosed" with loperamide "did so because they were misusing it or abusing it as an opioid substitute." The study was based on data from the "nationwide ToxIC registry for patients exposed to loperamide between 2011 and 2016." They found "26 cases of loperamide exposure (median age 27 years; 54% male) and found that the number and relative proportion of cases in the registry increased annually."

Open Forum

No items.

Next Meeting Date

The next meeting was scheduled for August 2, 2019.

Adjourn

There being no further business, the meeting was adjourned at 2:12 p.m.

Approved: *Mark Messer, D.O.*

Mark Messer, D.O., Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

Appendix

Appendix A – naloxone nasal spray New Drug Application and monograph
Appendix B – risperidone SQ LAI (Perseris®) New Drug Application and monograph
Appendix C – aripiprazole lauroxil (Aristada Initio®) New Drug Application and monograph
Appendix D – esketamine nasal spray (Spravato®) New Drug Application and monograph

415 — C
EXHIBIT A

APPENDIX 1: NEW DRUG APPLICATION FORM

TEXAS DEPARTMENT OF MENTAL HEALTH AND MENTAL RETARDATION

NEW DRUG APPLICATION

(for inclusion in the *DSHS/DADS Drug Formulary*)

** (THE NEW DRUG APPLICATION PROCESS IS DESCRIBED ON THE BACK OF THIS FORM.) **

Date: 1/17/19

Name of practitioner submitting the application: Elizabeth Deel

Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state school, state center, or local authority (state-operated community services (SOCS) or community MHMR center)):
Austin State Hospital

Information regarding new drug:

Therapeutic Classification	antidote
Generic Name	naloxone
Trade Name(s)	Narcan
Manufacturer(s)	Adapt Pharma Inc
Dosage Form(s)	Nasal spray

Explain the pharmacological action or use of this drug: Opioid antagonist for emergency treatment of known or suspected opioid overdose

Explain the advantages of this drug over those listed in the formulary: Only antidote for opioid overdose on formulary is the injection formulation not ideal for outpatient prescriptions & use

State which drugs this new drug would replace or supplement:
naloxone injection

****

☑ application is approved

signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete

signature of clinical/medical director or designee

Naloxone HCl
(NARCAN® Nasal Spray)

Classification: Antidote; Opioid Antagonist

Pharmacology:
Mechanism of Action: Naloxone hydrochloride is an opioid antagonist that competes and displaces opioids at mu-opioid receptors. It reverses the effects of opioids, including respiratory depression, sedation, hypotension, and psychomimetic and dysphoric effects.
Pharmacokinetics[1]**:**
Absorption: Intranasal (43.1%) Intramuscularly (54%)

	2 mg – One Nasal Spray in one nostril 20 mg/ml (N=29)	4 mg- One Nasal Spray in one nostril 40 mg/ml (N=29)	0.4 mg intramuscular injection (N=29)
T_{max} (h) ǂ	0.33	0.50	0.38
C_{max} (ng/mL)	2.91	4.83	0.88
$T_{½}$ (h)	1.85	2.08	1.24

ǂ T_{max} reported as median

Distribution: Relatively weak plasma protein binding (albumin).
Metabolism: Naloxone hydrochloride is primarily metabolized by glucuronide conjugation in the liver.
Elimination: Following one single intranasal administration of naloxone nasal spray, mean plasma half-life was 1.85 hours for 2mg and 2.08 hours for 4 mg. After oral or intravenous dose, about 25-45% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

Indications:
Naloxone nasal spray is intended for emergency treatment of known or suspected opioid overdose presenting with respiratory and/or central nervous system depression.
Naloxone nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present.
Naloxone nasal spray is not a substitute for emergency medical care.
Limitations of Use:
Restrict prescription of naloxone nasal spray 2 mg to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.

Administration:
Instruct prescription recipient to inform those around them about naloxone nasal spray and the *Instructions For Use*, emphasizing the following:

- No additional device assembly, priming, or testing required before use.
- Administer naloxone nasal spray as quickly as possible. Prolonged respiratory depression may result in central nervous system damage and death. It is important to seek emergency assistance immediately, even with use of naloxone nasal spray and continue surveilling the patient until emergency personnel arrive. Naloxone nasal spray is not a substitute for emergency medical care.
- Additional doses of naloxone nasal spray may be required until emergency medical assistance becomes available.
- Repeated sprays may be necessary for reversal of partial agonist or mixed agonist/antagonist agents (buprenorphine and pentazocine) due to longer duration of action.
- Do not attempt to reuse naloxone nasal spray. Each unit contains a single dose.
- Administer naloxone nasal spray in alternate nostrils with each dose.

Place patient in the supine position and provide support to the back of the neck, allowing the head to tilt back.

Dosage:
Initial dosing: In adults and pediatric patients, instill one spray into one nostril.
Repeat dosing: Seek emergency medical assistance after administration of first dose. Additional doses can be administered using a new naloxone nasal spray after 2 or 3 minutes if desired response is not achieved. Additional supportive and/or resuscitative measures may be helpful while waiting emergency medical assistance.

Contraindications:
Hypersensitivity to naloxone hydrochloride or any product ingredients.

Warning/Precautions:
- Duration of opioids may exceed naloxone nasal spray and return of respiratory and central nervous system depression may occur after initial improvement. Therefore, it is necessary to contact emergency medical assistance immediately after first dose.
- Reversal of partial agonists or mixed agonist/antagonists (buprenorphine and pentazocine) may be incomplete and require larger or repeat dosing. Buprenorphine antagonism is characterized by a gradual onset of reversal effects and a decreased duration of the prolonged respiratory depression.
- Use of naloxone nasal spray in opioid dependent individuals can precipitate withdrawal symptoms (body aches, diarrhea, tachycardia, fever, runny nose, nausea or vomiting, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure).

- In opioid dependent neonates, avoid abrupt precipitation of opioid withdrawal. Use of alternative naloxone-containing products that can be dosed according to weight and titrated to effect are preferred. Neonatal withdrawal symptoms include: convulsions, excessive crying, and hyperactive reflexes.
- Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, tremulousness, tachycardia, hypertension, seizure, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that have similar adverse cardiovascular effects.

Interactions:
Concurrent use with other opioid receptor antagonist (naldemedine, naloxegol, methylnaltrexone) may enhance the adverse/toxic effects (i.e. risk for opioid withdrawal).

Adverse Reactions:
In clinical trials, healthy adult volunteers who received 1 or 2 sprays of naloxone nasal spray reported increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, rhinalgia, and xeroderma.

Use in Special Population:
There is limited available data on naloxone hydrochloride use in pregnant women and is insufficient to inform a drug associated risk. In animal studies, no embryotoxic or teratogenic effects have been observed. Naloxone hydrochloride can cross the placenta and precipitate withdrawal in the fetus. Careful monitoring is recommended until the mother and fetus are stabilized. Currently there is no information regarding presence of naloxone in human milk or effects on the breastfed infant or on milk production. Studies have shown that naloxone does not affect prolactin or oxytocin hormone levels.

HHSC Cost:
Narcan® Nasal Spray 4 mg/0.1 ml (2 pack): $125.00
Evzio® Auto-Injector 2 mg/0.4 ml (2 pack): $4,100
Naloxone hydrochloride 0.4 mg/1 ml vial: $6.63

Monitoring:
- Respiratory rate
- Heart rate
- Blood pressure
- Temperature
- Level of consciousness
- Oxygen saturation

Product Identification:
Naloxone nasal spray 4 mg is supplied as a carton containing two blister packages each with a single spray device.

Efficacy:
Naloxone has been proven to reverse opioid overdoses and many major opioid authorities and governing bodies have released statements encouraging the practice of co-prescribing naloxone with opioid prescriptions for at risk populations. The CDC's 2016 *Guideline for Prescribing Opioids for Chronic Pain* recommends clinicians to incorporate management plan strategies to mitigate risk, such as offering naloxone, to those with increased risk of opioid overdose.[3] Increased risk factors for opioid overdose include history of overdose, history or substance use disorder, higher opioid dosages (>50 MME/day) or concurrent benzodiazepine use. After the Surgeon General's Advisory on naloxone was announced, the American Academy of Pain Medicine released a secondary statement supporting use of naloxone as an important tool in response to the opioid epidemic.[4,5] The World Health Organization in 2018 released an information sheet on opioid overdose in support of countries promoting naloxone availability and monitoring drug trends, as well as training and management of opioid overdose.[6]
In 2016, the National Institute on Drug Abuse funded a large study to evaluate feasibility and impact of co-prescribing naloxone in patients on long-term opioid therapy. Authors found patients who received a naloxone prescription had 47% fewer opioid related ED visits per month six months after receiving naloxone and 63% fewer visits after one year (compared to those who did not receive naloxone).[7] In a follow up study, it was found that 87% of patients had successfully filled the naloxone prescription and most patients had either positive or neutral response to being offered naloxone.[8]
Smaller studies in communities have shown promising results with Opioid Overdose Education & Naloxone Distribution (OEND) programs. In Chicago, a 2006 study showed reversal (20% decrease) of a previous steadily increasing trend of heroin overdose deaths since 1991.[9] In Massachusetts, opioid overdose death rates were shown to be reduced in communities where OEND programs were implemented.[10] The study compared opioid overdose mortality rates of 19 different communities with varying implementation rates. Low implementation (1-100 people trained per 100,000 population) and high implementation (greater than 100 people trainer per 100,000 population) showed 27% and 46% reduction of opioid related mortality rates.

Conclusions:
Naloxone nasal spray is an inexpensive, effective, and accessible option to protect patients at risk for opioid overdose without the injection burden of other naloxone formulations. This formulation allows medically untrained people, close friends/family members at the emergency scene, to safely and effectively reverse overdoses without having undergone aseptic technique training and risk of being exposed to needle stick injuries. It also shows similar and comparable pharmacokinetic properties to the intramuscular formulation. The only naloxone product currently on formulary is an injectable formulation and not a suitable option for patients discharging to the community setting. The Texas Pharmacy Association has obtained a physician signed standing order to facilitate the prescribing process of naloxone to increase accessibility for patients at risk. Naloxone nasal spray is not intended for every patient discharged on opiates. Providers should identify recipients based on risk factors outlined in the CDC Opioid Prescribing guidelines (history of overdose, substance use disorder, >50 MME/day, and/or concurrent

benzodiazepine use). In conclusion, addition of naloxone nasal spray is recommended for formulary approval given current opioid guideline recommendations, supported evidence for decrease in opioid related deaths, and ideal formulation for outpatient use with similar pharmacokinetic efficacy as naloxone injection and is less expensive than the naloxone auto-injector.

Recommendation:
Recommend for addition to formulary.

References:

1. Product Information: NARCAN® Nasal Spray. Adapt Pharma Inc., Radnor, PA, 2017. Revised February 2017.
2. Lexi-Drugs. Lexicomp [Internet]. Hudson, OH: Wolters Kluwer Health, Inc. 1978-2018. Naloxone; [cited 2018 Jan 15]. Available at http://online.lexi.com.
3. Center for Disease Control and Prevention. Guideline for prescribing opioids for chronic pain. Available at: www.cdc.gov/drugoverdose/prescribing/guideline.html.
4. Surgeon General's Advisory on Naloxone and Opioid Overdose. U.S. Department of Health and Human services. Available at: https://www.surgeongeneral.gov/priorities/opioid-overdose-prevention/naloxone-advisory.html.
5. Opioid Task Force Naloxone Update. American Medical Association. 2017.
6. World Health Organization Information Sheet on Opioid Overdose. Available at: http://www.who.int/substance_abuse/information-sheet/en/.
7. Coffin PO, Behar E, Rowe C, et al. Nonrandomized Intervention Study of Naloxone Coprescription for Primary Care Patients Receiving Long-Term Opioid Therapy for Pain. Ann Intern Med. 2016;165(4):245-52.
8. Behar E, Rowe C, Santos GM, Murphy S, Coffin PO. Primary Care Patient Experience with Naloxone Prescription. Ann Fam Med. 2016;14(5):431-6.
9. Maxwell S, Bigg D, Stanczykiewicz K, et al. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. J Addict dis. 2006;25(3):89-96.
10. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ. 2013;346:f174. Published 2013 Jan 31. doi:10.1136/bmj.f174

Prepared by:
Melanie Chang, Pharmacy Student Intern
Austin State Hospital
January 2019

Reviewed by:
Lisa Mican, Pharm.D., BCPP
Clinical Pharmacist
Austin State Hospital
January 2019

APPENDIX 1: NEW DRUG APPLICATION FORM

Texas IIHS Health and Specialty Care System

NEW DRUG APPLICATION

(for inclusion in the *State Operated Facilities Drug Formulary*)

Date: 3/4/19

Name of practitioner submitting the application: Mark Messer DO.

Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state supported living center, state center, or local authority (state-operated community services (SOCS) or community MHMR center)):

Information regarding new drug:

Therapeutic Classification	Antipsychotic
Generic Name	Risperidone
Trade Name(s)	Perseris
Manufacturer(s)	Indivior
Dosage Form(s)	90 mg & 120 mg

Explain the pharmacological action or use of this drug

Explain the advantages of this drug over those listed in the formulary:

State which drugs this new drug would replace or supplement:

****

☐ application is approved

signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete

signature of clinical/medical director or designee

Risperidone Extended Release Injection
(Perseris®)

Classification: Atypical antipsychotic drug

Pharmacology[1-3]:
Perseris® clinical effect is due to combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone. Risperidone is a monoaminergic antagonist with high affinity for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α1 and α2 adrenergic, and H_1 histaminergic receptors. The drug's therapeutic activity for schizophrenia is mediated largely through $5HT_2$ and D_2 receptor antagonism. Excessive dopamine in the brain activates the mesolimbic pathway and contributes to positive symptoms such as delusions, hallucinations, and thought disorders. By blocking the dopamine receptors in the brain, Perseris® effectively helps reduce the positive symptoms associated with schizophrenia. Serotonin plays a role in behavior, affect and motor activity; abnormalities in serotonin transmission are responsible for the negative symptoms. By blocking serotonin receptors, Perseris® effectively helps alleviate negative symptoms, which disturb the patient's emotions and behavior. Atypical antipsychotic medications were developed to reduce the incidence of extrapyramidal symptoms (EPS) associated with first generation antipsychotics, which mainly block D_2 receptors.

Pharmacokinetics[1]:

Absorption	**Following subcutaneous injection, a depot of risperidone forms and provides sustained plasma levels over a monthly interval. After injection, two peaks are observed with similar magnitude. The first peak occurs with a T_{max} of 4 to 6 hours, due to initial release of drug. The second peak is seen at 10 to 14 days post-dose and is due to slow release from the depot. For 9-hydroxyrisperidone, the T_{max} is 6 to 48 hours and second peak is between 7 to 11 days.**
Distribution	Volume of distribution is large due to depot injection. Risperidone is bound to albumin and α1-acid glycoprotein, its plasma protein binding is about 90%, while 9-hydroxyrisperidone's is 77%. Neither of the two displace each other from plasma binding sites.
Metabolism	Metabolized by the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by CYP2D6 with small contribution by CYP3A4. Another minor pathway is N-dealkylation. Both risperidone and 9-hydroxyrisperidone have similar pharmacological activity, therefore the clinical effect is due to combined concentrations of both. No dose adjustment is necessary based on CYP2D6 genotype as plasma exposure to risperidone and 9-hydroxyrisperidone were similar in CYP2D6 extensive, intermediate and poor metabolizers.
Excretion	Eliminated primarily in the urine, to a lesser extent in the feces. The terminal half-life of risperidone is between 9 to 11 days, the terminal half-life of 9-hydroxyrisperidonee is 8 to 9 days.

Indications[1]:
Perseris® is indicated for the treatment of schizophrenia in adults.

Dosage[1]:
Recommended to initiate at a dose of either 90 mg or 120 mg once monthly by subcutaneous injection. Do not administer more than one dose (90 mg or 120 mg total) per month. Perseris® 90 mg corresponds to 3 mg/day of oral risperidone and Perseris® 120 mg corresponds to 4 mg/day oral risperidone.
Co-Administration with Strong 2D6 Inhibitors: When fluoxetine or paroxetine is considered, place patient on lower Perseris dose two to four weeks before planned start date of fluoxetine or paroxetine to adjust for expected increase in plasma concentration of risperidone. When fluoxetine or paroxetine is initiated in patients receiving Perseris 90mg, continuation of treatment is recommended unless clinical judgment necessitates otherwise.

Co-Administration with Strong CYP 3A4 inducers: Monitor patient closely for first four to eight weeks if carbamazepine or other known hepatic inducers initiated. Patients receiving Perseris 90 mg, consider dose increase to 120mg and in patients already receiving 120mg dose, additional oral risperidone may need to be considered. Upon discontinuation of strong CYP 3A4 inducers, the dose of Perseris or any additional oral risperidone therapy should be re-evaluated to account for increase in plasma risperidone concentration.

Contraindications[1]:
- Hypersensitivity to risperidone, its metabolite, 9-hydroxyrisperidone, or any of its components (poly DL-lactide-co-glycolide polymer and *N*-methyl-2-pyrrolidone)

Precautions[1]:
- Increased mortality in elderly patients with dementia-related psychosis
- Can cause cerebrovascular adverse reactions (stroke, transient ischemic attack) in elderly patients with dementia-related psychosis
- Can cause a potentially fatal symptom complex known as neuroleptic malignant syndrome (NMS)
- Can cause syndrome of potentially irreversible, involuntary, dyskinetic movements known as tardive dyskinesia
- Has been associated with metabolic changes including hyperglycemia, dyslipidemia, and body weight gain which can increase cardiovascular and cerebrovascular risk
- Use with caution in patients diagnosed with diabetes mellitus as ketoacidosis and hyperosmolar coma or death have occurred from blood glucose changes
- Can cause hyperprolactinemia which may lead to galactorrhea, amenorrhea, gynecomastia, impotence and over time decreased bone mineral density
- Anaphylactic reactions and angioedema to risperidone and 9-hydroxyrisperidone have been reported
- Use caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to

hypotension (dehydration and hypovolemia) as orthostatic hypotension has occurred
- Use caution in elderly patients aged 65 years or older as Perseris® was not studied in them
- Can cause falls and should be used with caution in patients with elevated risk of falls
- Can cause or worsen pre-existing leukopenia, neutropenia and agranulocytosis
- Potential to impair judgement, thinking, or motor skills; patients should use caution until they are certain it does not affect them adversely in these areas
- Use caution in patients with history of seizures as risperidone can potentially lower the seizure threshold and lead to increased seizures
- Use caution in patients at risk of aspiration pneumonia as esophageal dysmotility and aspiration has occurred
- Can cause priapism, severe cases may require surgical intervention
- Use caution when prescribing to patients exposed to temperature extremes as both hypothermia and hyperthermia have occurred
- Neonates exposed to antipsychotic drugs during the third trimester are at risk for EPS or withdrawal symptoms following delivery
- Not studied in renal or hepatic impairment

Interactions[1]:
Interactions of Perseris® with other drugs has not been studied. All interaction data currently available is based on studies with oral risperidone. Concomitant use with strong CYP2D6 inhibitors may increase exposure of risperidone and decrease exposure of 9-hydroxyrisperidone, the active metabolite. Examples of these include paroxetine, fluoxetine and quinidine. Concomitant use with strong CYP3A4 inducers may decrease concentrations of both risperidone and its active metabolite, 9-hydroxyrisperidone, leading to decreased efficacy. Examples of these include rifampin, carbamazepine, phenytoin and phenobarbital. Use with centrally-acting drugs and alcohol will lead to additive pharmacological effects and can increase nervous system disorders. Examples include antipsychotics and alcohol. Concomitant use with hypotensive agents can enhance the hypotensive effects of other therapeutic agents with hypotensive effects. Examples include Angiotensin Converting Enzyme (ACE) inhibitors, beta-blockers and diuretics. Perseris® may antagonize the pharmacologic effects of dopamine agonists such as carbidopa and levodopa.

Adverse Reactions[1]:
Adverse reactions from Perseris® have been reported from one double-blind, placebo-controlled study containing 814 adult subjects. The adverse reactions occurring in $\geq$ 5% in any Perseris®-treated group and greater than placebo were weight gain, constipation, sedation/somnolence, pain in extremity, back pain, akathisia, anxiety, and musculoskeletal pain. There was no single adverse reaction leading to discontinuation that occurred at a rate of > 2% in Perseris®-treated patients and greater than placebo. Some adverse reactions occur or increase in severity based on dose, these include: increased weight, increased prolactin, EPS, dystonia, EKG changes, pain and injection site reactions. Increasing the dose increases the likelihood and severity of the aforementioned adverse reactions.

Cost Comparison:

Name	Generic ?	Strength (mg)	Cost[a]	Monthly Cost ($)
Risperidone (Perseris®)	No	90	1710.00	1710.00
Risperidone (Perseris®)	No	120	2280.00	2280.00
Risperidone (Risperdal®)	Yes	0.25, 0.5, 1, 2, 3, 4	0.15 (3mg), 0.16 (4mg)	4.50 (3mg), 4.80 (4mg)
Risperidone (Risperdal Consta®)	No	12.5, 25, 37.5, 50	443.564 (25mg)	887.128 (25mg)
Risperidone (Risperdal M-Tab®)	Yes	0.25, 0.5, 1, 2, 3, 4	1.078 (3mg), 1.431 (4mg)	32.34 (3mg), 42.93 (4 mg)
Paliperidone palmitate (Invega Sustenna®)	No	39, 78, 117, 156, 234	1223.511 (117mg), 1631.417 (156mg)	1223.511 (117mg), 1631.417 (156mg)

[a]Hospital acquisition cost, per unit (in US dollars)

Product Identification and administration[1]:
90 mg kit has NDC 12496-0090-01
120 mg kit has NDC 12496-0120-01
Store in a refrigerator at 2° to 8°C, allow at least 15 minutes for kit to come to room temperature prior to mixing. Unmixed kits are good for 7 days at room temperature.
Supplied in a single-dose kit, packaged in a carton containing:

- One pouch with a sterile syringe prefilled with risperidone powder (labelled 'P')
- One pouch with a sterile syringe prefilled with the delivery system and desiccant (labelled 'L')
- One 18-gauge, 5/8-inch sterile safety needle

Mix liquid into powder and back, premix 5 cycles gently and mix an additional 55 cycles more vigorously.
Administer subcutaneously in the abdomen only, belt line should be avoided. Pinch skin away from muscle, inject at 45-degree angle, area should not be rubbed, lump disappears over few weeks

Efficacy[4-6]:
Efficacy of Perseris® was demonstrated in two randomized trials. One being an 8-week, randomized, double-blind, placebo-controlled study, NCT #02109562. This study compared Perseris® 90 mg and 120 mg subcutaneous injections every 4 weeks with placebo in adults experiencing acute exacerbations of schizophrenia. Patients must have a Positive and Negative Syndrome Scale (PANSS) total score of 80 to 120 at the screening visit. The primary endpoint was the change in PANSS total score from baseline to end of study. Both formulations of Perseris® showed statistically significant improvement compared with placebo. The 90 mg dose saw a

mean change from baseline of -19.86, while the placebo was -6.50 (CI -10.87, -2.13). The 120 mg dose saw a mean change from baseline of -23.61, while the placebo was -10.24 (CI -14.64, -5.85). Both formulations of Perseris® demonstrated statistically significant improvement for the secondary efficacy endpoint as well, which was defined as the CGI-S score at Day 57.

The second study was a phase II randomized, double-blind, placebo-controlled and active-controlled study, NCT #01499563. This study compared Perseris®, ITI-007, 60 mg and 120 mg, with oral risperidone and placebo in acutely psychotic adults with schizophrenia. The primary outcome was the PANSS total score. This study showed Perseris® 60mg to have antipsychotic efficacy superiority over placebo in the primary endpoint, but not for 120 mg. It also showed improvements in negative and depression symptoms compared with placebo. Overall, it indicated Perseris® as effective therapy.

Safety[1,4-6]:

Body Weight and BMI

During the clinical trial, all subjects gained weight. The placebo group had a mean weight gain of 2.835 kg, the 90 mg group had 5.148 kg, and the 120 mg group had 4.69 kg. According to guidelines, a 7% or greater increase in weight is considered significant. In the study, both treatment groups had higher incidence of subjects with 7% or greater weight gain compared with placebo. It was 32.7% in the 90 mg group, 42.1% in the 120 mg group and 18% in the placebo group. A 10% or greater increase in weight was also reported, the incidence of subjects in the 90 mg group was 19.6%, 120 mg group was 19.3%, and placebo was 5.4%. Although the percent weight gains were different between groups, the mean differences in BMI from baseline to the end of the study were similar between all three groups.'

Hyperprolactinemia

Increased prolactin levels in both male and female subjects occurred in both treatment groups compared with placebo during the clinical trial. The differences were found to be dose dependent as greater increases were observed in the 120 mg group than in the 90 mg group. Females were noted to have more pronounced elevation in prolactin levels compared to males in this 8week double blind placebo controlled trial

Carcinogenesis

No carcinogenicity studies were done with the subcutaneous injections, oral risperidone has conducted carcinogenicity studies in mice and rats. These studies found statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas. These increases are considered prolactin-mediated.

Mutagenesis

No evidence of mutagenic potential was observed in and in vivo micronucleus test in rats. The safety margin of risperidone was 13 times the delivery system amount present in monthly 120 mg risperidone.

Cardiovascular

No clinically relevant differences in EKG intervals at rest in either treatment group compared with placebo. The incidence of Bazett-corrected QT (QTcB) interval increases from baseline of 30 milliseconds or greater was higher for both treatment groups than placebo. The 90 mg group had 7-12% incidence, while the 120 mg group had 6-14% and placebo was 3-6%. Although this difference was seen, it was not statistically significant. No subjects in the trial had a QTc interval of 500 milliseconds or greater.

Conclusions[1,4,6]:
Perseris® has been shown to be safe and effective in clinical trials. A few trials have documented efficacy for both 90 mg and 120 mg injections when compared to placebo. There have been no studies showing superiority of Perseris® to oral risperidone or other injectable antipsychotics. Side effect profile for the injection is similar to oral risperidone.

Recommendation:
Overall, current data suggests no advantage of Perseris® over other long acting injectable antipsychotic medications. There are no trials comparing Perseris® with other available long acting injectable antipsychotics at this time. Perseris® appears to have similar effects of other second-generation antipsychotics. It is slightly different as it is the only subcutaneous injectable antipsychotic. It is also the only risperidone injectable formulation administered monthly instead of every two weeks. However, there are other injectable antipsychotics administered monthly, Invega Sustenna® is one example. Perseris® cost is significantly higher than other comparable alternatives and its dosing maximum is lower than the typical total daily dose needed to manage schizophrenia. At this time, the addition of Perseris® to formulary is not recommended due to similarity with other treatment options, lack of achieving comparable dosing to higher oral risperidone doses and increased cost of use.

References:

1) Package insert: Perseris®, risperidone extended-release injection. Indivior, Inc., North Chesterfield, VA. Last revised July 2018.

2) O'Connor F. The Role of Serotonin and Dopamine in Schizophrenia. J Am Psychiatr Nurses Assoc. 1998:4(4):30-34.

3) Patel KR, Cherian J, Gohil K, et al. Schizophrenia: Overview and Treatment Options. Pharm Ther. 2014:39(9):638-645.

4) Lieberman JA, Davis RE, Correll CU, et al. ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial. Biol Psychiatry. 2016:79:951-961.

5) Citrome L. Sustained-Release Risperidone via Subcutaneous Injection: A Systemic Review of RBP-7000 (Perseris®) for the Treatment of Schizophrenia. Clin Schizophr Relat Psychoses. 2018:12(3):130-141.

6) Nasser AF, Henderson DC, Fava M, et al. Efficacy, Safety, and Tolerability of RBP-7000 Once-Monthly Risperidone for the Treatment of Acute Schizophrenia. J Clin Psychopharmacol. 2016:36(2):130-140.

Prepared by:
Cassidy Mayo, Pharmacist Intern
P4 APPE Rotation Psychiatric Elective
Austin State Hospital

Reviewed by:
Rania Kattura, PharmD, MS, BCPP
Clinical Psychiatric Pharmacist
Austin State Hospital

March 2019

APPENDIX 1: NEW DRUG APPLICATION FORM

Texas IIIS Health and Specialty Care System

NEW DRUG APPLICATION

(for inclusion in the State Operated Facilities Drug Formulary)

Date: 1/2/19

Name of practitioner submitting the application: Mark Messer D.O.

Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state supported living center, state center, or local authority (state-operated community services (SOCS) or community MHMR center)):

Information regarding new drug:

Therapeutic Classification	Antipsychotic
Generic Name	Aripiprazole Lauroxil
Trade Name(s)	Initio (Aristada)
Manufacturer(s)	Alkermes
Dosage Form(s)	IM

Explain the pharmacological action or use of this drug

Pro-drug of Aripiprazole, D2partial agonist + 5HT2A antagonist

Explain the advantages of this drug over those listed in the formulary:

Longer intervals between injections (8wks)

State which drugs this new drug would replace or supplement:

****

☐ application is approved

OR

☑ application is appropriate and complete

signature of chairman of facility pharmacy and therapeutics committee

signature of chief medical director or designee

Aripiprazole lauroxil
(Aristada Initio™)

Classification: Atypical Antipsychotic

Pharmacology:[1]
Aristada Initio (aripiprazole lauroxil) is a prodrug of aripiprazole. Following intramuscular injection, aripiprazole lauroxil is likely converted by enzyme-mediated hydrolysis to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole. The mechanism of action of aripiprazole in schizophrenia is unclear. However, efficacy could be mediated through a combination of partial agonist activity at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. [1]

Pharmacokinetics:[1]

Absorption	Following a single intramuscular injection of Aristada Initio, the appearance of aripiprazole in systemic circulation occurs on the day of injection; the median time to reach peak plasma exposure is approximately 27 days (range: 16-35 days). With the addition of a single intramuscular injection of Aristada Initio and 30mg oral aripiprazole at the time of the first Aristada dose, aripiprazole concentrations reach relevant levels within 4 days. Aripiprazole exposure was similar for deltoid and gluteal intramuscular injections of Aristada Initio.
Distribution	Based on population pharmacokinetic analysis, the apparent volume of distribution of aripiprazole following intramuscular injection of ARISTADA was 268L, indicating extensive extravascular distribution following absorption. Aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5mg/day to 30 mg/day oral aripiprazole for 14 days, there was dose-dependent D2 receptor occupancy indicating brain penetration of aripiprazole in humans.
Elimination	The biotransformation of Aristada Initio likely involves enzyme-mediated hydrolysis to form *N*-hydroxymethyl-aripiprazole, which subsequently undergoes hydrolysis to aripiprazole. Elimination of aripiprazole is mainly through hepatic metabolism involving CYP3A4 and CYP2D6. For Aristada Initio, the mean aripiprazole terminal elimination half-life was 15-18 days after injection. The significantly longer aripiprazole apparent half-life compared to oral aripiprazole (mean 75 hours) is attributed to the dissolution and formation rate-limited elimination of aripiprazole following Aristada Initio administration.

Indications and Usage:[1]
- Aristada Initio, in combination with oral aripiprazole, is indicated for the initiation of Aristada when used for the treatment of schizophrenia in adults.[1]

Dosage and Administration:[1,2]

- Aristada Initio is only to be used as a single dose to initiate Aristada treatment or as a single dose to re-initiate Aristada treatment following a missed dose of Aristada. Aristada Initio is not for repeated dosing.
- After establishing tolerability with oral aripiprazole, administer the first Aristada intramuscular injection (441 mg, 662 mg, 882 mg, or 1064 mg) in conjunction with both:
    - One 675 mg injection of Aristada Initio in the deltoid or gluteal muscle (which corresponds to 459 mg of aripiprazole); **and**
    - One 30 mg dose of oral aripiprazole.
- Aristada Initio is not interchangeable with Aristada due to differing pharmacokinetic profiles.
- Aristada Initio is to be administered as an intramuscular injection by a healthcare professional.
- The first Aristada injection may be administered on the same day as Aristada Initio or up to 10 days thereafter.
- Avoid injecting both Aristada Initio and Aristada concomitantly into the same deltoid or gluteal muscle.
- For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with Aristada Initio. Due to the half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability. Refer to the prescribing information of oral aripiprazole for the recommended dosage and administration of the oral formulation.

Dosing for Missed Doses of Aristada:

Recommendation for Concomitant Supplementation Following Missed Doses of Aristada			
Dose of Patient's Last Aristada Injection	Length of Time Since Last Injection		
441 mg	≤6 weeks	>6 and ≤7 weeks	>7weeks
662 mg	≤8 weeks	>8 and ≤ 12 weeks	>12 weeks
882 mg	≤8 weeks	>8 and ≤ 12 weeks	>12 weeks
1064 mg	≤10 weeks	>10 and ≤ 12 weeks	>12 weeks
Dosage and Administration for Re-initiation of Aristada	No supplementation required	Supplement with a single dose of Aristada Initio OR 7 days of Oral Aripiprazole	Re-initiate with a single dose of Aristada Initio and a single dose of oral aripiprazole 30 mg OR supplement with 21 days of oral aripiprazole

Storage:[1]

Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F). Do not freeze.

Contraindications:[1]
Aristada Initio is contraindicated in patients with known hypersensitivity reaction to aripiprazole.

Precautions:[1]
- *Increased Mortality in Elderly Patients with Dementia-related Psychosis:* Aristada Initio is not approved for the treatment of patients with dementia-related psychosis.
- *Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia: Aristada Initio is not approved for the treatment of patients with dementia-related psychosis.*
- *Potential for Dosing and Medication Errors*: Substitution and dispensing errors between Aristada Initio and Aristada could occur. Do not substitute Aristada Initio for Aristada.
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation of antipsychotic drugs, symptomatic treatment, and close monitoring.
- *Tardive Dyskinesia*: Discontinue if clinically appropriate.
- *Metabolic Changes*: Monitor for hyperglycemia, dyslipidemia, and weight gain.
- *Pathological Gambling and Other Compulsive Behaviors*: Consider discontinuation of antipsychotic.
- *Orthostatic Hypotension*: Monitor heart rate and blood pressure and educate patients at increased risk of these adverse reactions or at an increased risk of developing complications from hypotension, including patients with dehydration, hypovolemia, treatment with antihypertensive medication, and history of cardiovascular or cerebrovascular disease.
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors.
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.
- *Potential for Cognitive and Motor Impairment*: Use caution when operating machinery.
- *Body Temperature Regulation*: Antipsychotics may disrupt the body's ability to reduce core body temperature.
- *Dysphagia*: Antipsychotic drug use has been associated with esophageal dysmotility and aspiration. Use caution in patients at risk for aspiration pneumonia.

Interactions:[1]

Drug Interaction	Example Medications	Clinical Impact	Management

Strong CYP3A4 Inhibitors and Strong CYP2D6 Inhibitors	Fluoxetine Paroxetine Itraconazole Clarithromycin Quinidine	Increased the exposure of aripiprazole	Avoid use of Aristada Initio
Strong CYP3A4 Inducers	Carbamazepine Rifampin	Decreased the exposure of aripiprazole	Avoid use of Aristada Initio
Antihypertensive Drugs	Carvedilol Lisinopril Prazosin	Enhanced effect of certain antihypertensive agents	Avoid use of Aristada Initio
Benzodiazepines	Lorazepam	Greater intensity of sedation when lorazepam and oral aripiprazole were combined. The orthostatic hypotension observed was greater with the combination compared to lorazepam alone.	Avoid use of Aristada Initio

Adverse Reactions:[1]
In pharmacokinetic studies, the safety profile of Aristada Initio was generally consistent with that observed for Aristada. Commonly observed adverse reactions with Aristada (aripiprazole lauroxil) occurring in ≥5% of the population and at least twice the rate of placebo in patients treated with aripiprazole lauroxil was akathisia. Reactions occurring at an incidence of 2% or more in aripiprazole lauroxil were: injection site pain, increased weight, increased blood creatinine phosphokinase, akathisia, headache, insomnia and restlessness.

In pharmacokinetic studies, the incidences of injection site reactions with Aristada Initio were similar to the incidence observed with Aristada (aripiprazole lauroxil). In Aristada trials, injection site reactions were reported by 4% of patients treated with 441 mg aripiprazole lauroxil and 5% of patients treated with 882 mg aripiprazole lauroxil compared to 2% of patients treated with placebo.

Use in special populations:[1]
Pregnancy: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There is limited published data on aripiprazole use in pregnant women. No teratogenicity was observed in animal reproductive studies with intramuscular administration of aripiprazole lauroxil to rats and rabbits during organogenesis at equivalent maximum recommended human dose. However, oral aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits. Pregnant women should be advised of the potential risk. A pregnancy exposure registry is available.

Lactation: Aripiprazole is present in human breast milk; however, there are insufficient data to assess the amount in human milk, the effects on the breastfed infant, or the effects on milk production. Risks and benefits should be weighed in women who breastfeed.

Pediatric use: Safety and effectiveness of Aristada Initio has not been established in pediatric patients.

Geriatric use: Safety and effectiveness of Aristada Initio has not been established in patients > 65 years of age.

CYP2D6 Poor Metabolizers: Avoid use of Aristada Initio in patients who are CYP2D6 poor metabolizers because dosage adjustments are not possible.

Hepatic Impairment: No dosage adjustment for mild to severe hepatic impairment (Child-Pugh score between 5 and 15).

Renal Impairment: No dosage adjustment for mild to severe renal function (glomerular filtration rate between 15 and 90 mL/minute).

Cost Comparison:

Dosage Form and Dose	Treatment Duration (days)	Unit Cost	Total Cost
Aristada Initio 675mg	1	$1,665.31	$1666.99
Aripiprazole 30 mg orally	1	$1.68	
Aripiprazole 20mg orally	21	$1.72	$36.12

Monitoring:[3]

- Improvement in signs and symptoms of schizophrenia indicates efficacy
- Need for continued treatment: evaluate periodically
- Fasting glucose: baseline and periodically in patients with risk factors for diabetes mellitus and in any patient who develops symptoms of hyperglycemia during treatment
- Worsened glucose control: regularly in patients with diabetes mellitus
- CBC: frequently during the first few months in patients with a history of low WBC or absolute neutrophil count, and in those with a history of drug-induced leukopenia or neutropenia
- Dyslipidemia and/or weight gain
- Orthostatic vital signs, including heart rate and blood pressure: in patients who are antipsychotic-naïve, or at risk of complications from hypotension (e.g., dehydration, hypovolemia, concomitant use of antihypertensives, those with a history of cardiovascular or cerebrovascular disease)
- Fall risk assessment: high risk patients, especially the elderly when initiating treatment and recurrently in patients on long term therapy

Efficacy:[4,5]

One pharmacokinetic bridging study was performed to determine if aripiprazole concentrations with Aristada Initio, one aripiprazole 30 mg oral tablet, and the Aristada injection would be comparable to Aristada treatment initiated with 21 days

of oral aripiprazole overlap. This 1-day regimen was designed to achieve plasma aripiprazole concentrations in the therapeutic range within 4 days, which is consistent with the 21 day oral initiation regimen indicated in the Aristada prescribing information. This was a 6-month, double-blind, placebo-controlled, phase 1 study in patients with schizophrenia. Patients were randomized to receive one of the following four treatments:

1. 441 mg Aristada +
   662 mg aripiprazole lauroxil nanocrystalline dispersion +
   30 mg oral aripiprazole once

2. 441 mg Aristada +
   15 mg oral aripiprazole x 21 days

3. 882 mg Aristada +
   662 mg aripiprazole lauroxil nanocrystalline dispersion +
   30 mg oral aripiprazole once

4. 882 mg Aristada +
   15 mg oral aripiprazole x 21 days

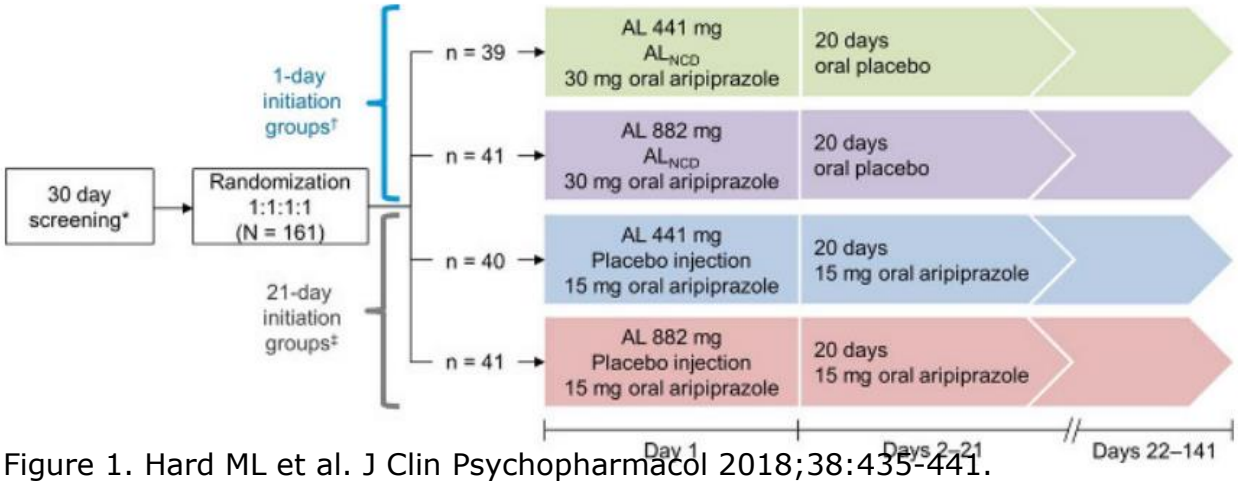

Figure 1. Hard ML et al. J Clin Psychopharmacol 2018;38:435-441.

Blood samples for liquid chromatography-tandem mass spectrometry were collected for analysis within 1 hour predose and 1, 2, 3, 4, 5, and 8 hours (+/- 15 minutes) postdose on day 1. On post initiation days 2 to 21, a single sample was collected before oral aripiprazole (or oral placebo) administration. On day 21, samples were collected at the same time frames as on day 1. Further samples were collected up to day 141.

133 patients completed the study. Results from the 1-day initiation regimen groups showed mean plasma aripiprazole concentrations and exposures within the first month that were comparable to those of the 21-day initiation regimen groups (Figure 2). This study shows that the 1-day initiation regimen is a suitable alternative option to the current 21 days of oral aripiprazole overlap for starting Aristada.

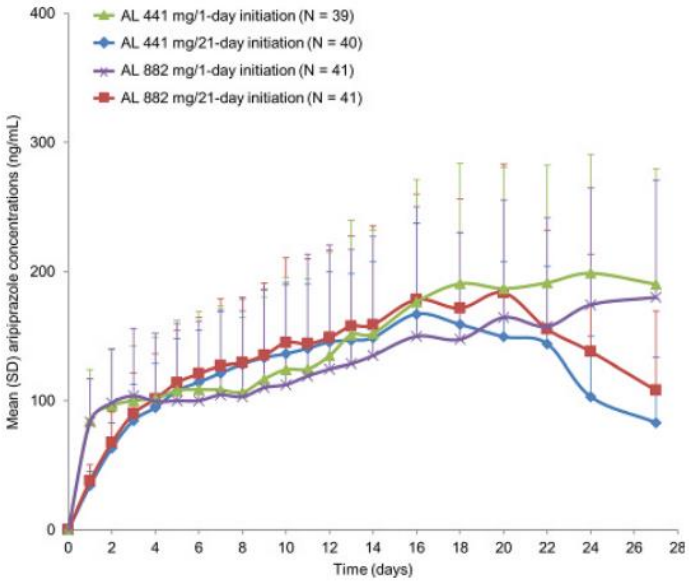

Figure 2. Hard ML et al. J Clin Psychopharmacol 2018;38:435-441.

Another study developed a population pharmacokinetic model to describe aripiprazole pharmacokinetics following administration of aripiprazole lauroxil nanocrystalline dispersion, aripiprazole lauroxil, and oral aripiprazole. In this study, researchers used 12,768 plasma aripiprazole concentrations from 343 patients (from 4 previous clinical studies) for the analysis and to construct the model. Based on these models, the authors concluded that the 1-day initiation regimen (Aripiprazole Initio + 30 mg oral aripiprazole) with all approved Aristada dosing regimens is predicted to achieve aripiprazole concentrations associated with therapeutic doses of Aristada using the 21-day initiation regimen within 4 days. This model was also used to determine that the first Aristada injection can be given up to 10 days after the 1-day initiation regimen, and that Aristada Initio can be used to re-establish concentrations associated with missed doses of Aristada.

Conclusions:
Aristada Initio 675 mg, in combination with one dose of 30 mg oral aripiprazole and the first dose of Aristada, offers the advantage of achieving therapeutic levels rapidly and eliminates the need for oral aripiprazole supplementation for 21 days when starting Aristada. This 1-day initiation regimen of aripiprazole lauroxil will be particularly beneficial for patients with schizophrenia with medication adherence issues, although the significant cost of Aristada Initio should be considered. The adverse effects with Aristada Initio are consistent with those seen with Aristada.

Recommendation:
Consider the addition of Aristada Initio to the formulary as it may be a beneficial initiation option for patients starting Aristada. If added, recommend adding it in "Reserve Drug" status due to cost with the condition that it be used only for patients whose anticipated length of inpatient stay is less than 3 weeks from the first dose of Aristada.

References:

1. Product Information: ARISTADA INITIO™ extended release injectable suspension for intramuscular use. Alkermes Inc., Waltham, MA, 2018.

2. Product Information: ARISTADA® extended release injectable suspension for intramuscular use. Alkermes Inc., Waltham, MA, 2018.

3. In Depth Answers; www.Micromedex.com. Greenwood Village (CO): Truven Health Analytics; 2017; March 11, 2019

4. Hard ML, Wehr AY, Du Y, Weiden PJ, Walling D, von Moltke L. Pharmacokinetic evaluation of a 1-day treatment initiation option for starting long-acting aripiprazole lauroxil for schizophrenia. J Clin Psychopharmacol. 2018;38: 435-441.

5. Hard ML, Wehr AY, Sadler BM, Mills RJ, von Moltke L. Population pharmacokinetic analysis and model-based simulations of aripiprazole for a 1-day initiation regimen for the long-acting antipsychotic aripiprazole lauroxil. Eur J Drug Metab Pharmacokinet. 2018;43: 461-469.

Prepared by:

Shelby Adams
Pharm.D. Candidate 2019
University of Texas at Tyler Fisch College of Pharmacy

Haley Holley
Pharm.D. Candidate 2019
University of Texas at Tyler Fisch College of Pharmacy

Edited and Reviewed by:

Brittany Parmentier, Pharm.D., BCPS, BCPP
Clinical Assistant Professor
University of Texas at Tyler Fisch College of Pharmacy

APPENDIX 1: NEW DRUG APPLICATION FORM
Texas HHS Health and Specialty Care System

NEW DRUG APPLICATION

(for inclusion in the *State Operated Facilities Drug Formulary*)

Date: 3/19/19

Name of practitioner submitting the application: Mark Messer D.O.

Name of entity with which the practitioner is associated by employment or contract (i.e., state hospital, state supported living center, state center, or local authority (state-operated community services (SOCS) or community MHMR center)):

Information regarding new drug:

Therapeutic Classification	
Generic Name	esketamine nasal spray
Trade Name(s)	Spravato®
Manufacturer(s)	Janssen
Dosage Form(s)	nasal spray

Explain the pharmacological action or use of this drug

Explain the advantages of this drug over those listed in the formulary:

State which drugs this new drug would replace or supplement:

****

☐ application is approved

signature of chairman of facility pharmacy and therapeutics committee

OR

☐ application is appropriate and complete

signature of Clinical/medical Director or designee

Esketamine (Spravato ®)

INDICATIONS AND USAGE

SPRAVATO is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults **(approved March 5, 2019).**

Limitations of Use

SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

Black Box Warning

Sedation

Patients are at risk for sedation after administration of SPRAVATO

Dissociation

Patients are at risk for dissociative or perceptual changes after administration of SPRAVATO.

Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Abuse and Misuse

SPRAVATO has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse.

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. SPRAVATO is not approved in pediatric patients.

LIST PRICE

56 mg dose = $590
84 mg dose = $885

CLINICAL PHARMACOLOGY

Mechanism of Action

Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Compared to the R-enantiomer, esketamine has a higher affinity for the NMDA receptor. The precise mechanism by which esketamine exerts its antidepressant effect is unknown. Proposed mechanisms of ketamine's

antidepressant action include NMDA receptor modulation, AMPA receptor activation, GABAergic interneuron disinhibition, direct effects of its hydroxyl-norketamine (HNK) metabolites, and numerous downstream actions.

Pharmacodynamics

Cardiac Electrophysiology

The effect of SPRAVATO (84 mg nasal spray and 0.8 mg/kg esketamine intravenously infused over 40 minutes) on the QTc interval was evaluated in a randomized, double-blind, placebo-, and positive-controlled (moxifloxacin 400 mg), 4-period, crossover study in 60 healthy subjects. A large increase in heart rate (i.e. >10 bpm) was observed in both intranasal and intravenous esketamine treatment groups. **The totality of evidence from the nonclinical and clinical data indicates a lack of clinically relevant QTc prolongation at the therapeutic dose of esketamine.**

Pharmacokinetics

The mean absolute bioavailability is approximately 48% following nasal spray administration.

The time to reach maximum esketamine plasma concentration is 20 to 40 minutes after the last nasal spray of a treatment session.

Mean terminal half-life ranges from 7 to 12 hours

Esketamine is primarily metabolized to nor-esketamine via CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19. Nor-esketamine is metabolized via CYP-dependent pathways; certain metabolites undergo glucuronidation. **Nor-esketamine is also a NMDA receptor antagonist but has less affinity for the receptor than does esketamine.**

Less than 1% of a dose of nasal esketamine is excreted as unchanged drug in urine. Following intravenous or oral administration, esketamine-derived metabolites were primarily recovered in urine ($\geq$ 78% of a radiolabeled dose) and to a lesser extent in feces ($\leq$2% of a radiolabeled dose).

No significant differences in the PK of SPRAVATO nasal spray were observed for sex and total body weight (>39 to 170 kg) based on population PK analysis. There is no clinical experience with SPRAVATO nasal spray in patients on renal dialysis or with severe (Child-Pugh class C) hepatic impairment. There is no dose adjustment for body weight, sex, renal impairment, hepatic impairment or nasal congestion.

DOSAGE AND ADMINISTRATION

Important Considerations Prior to Initiating and During Therapy

SPRAVATO must be administered under the direct supervision of a healthcare provider. A treatment session consists of nasal administration of SPRAVATO and post-administration observation under supervision.

Blood Pressure Assessment Before and After Treatment

Assess blood pressure prior to dosing with SPRAVATO.

If baseline blood pressure is elevated (e.g., >140 mmHg systolic, >90 mmHg diastolic), consider the risks of short term increases in blood pressure and benefit of

SPRAVATO treatment in patients with TRD. Do not administer SPRAVATO if an increase in blood pressure or intracranial pressure poses a serious risk.

After dosing with SPRAVATO, reassess blood pressure at approximately 40 minutes (which corresponds with the C_{max}) and subsequently as clinically warranted.

If blood pressure is decreasing and the patient appears clinically stable for at least two hours, the patient may be discharged at the end of the post-dose monitoring period; if not, continue to monitor.

Food and Liquid Intake Recommendations Prior to Administration
Because some patients may experience nausea and vomiting after administration of SPRAVATO, advise patients to avoid food for at least 2 hours before administration and to avoid drinking liquids at least 30 minutes prior to administration.

Nasal Corticosteroid or Nasal Decongestant
Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should administer these medications at least 1 hour before SPRAVATO.

Recommended Dosage
Administer SPRAVATO in conjunction with an oral antidepressant (AD).

The recommended dosage for SPRAVATO is shown in Table 1. Dosage adjustments should be made based on efficacy and tolerability. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.

Table 1: Recommended Dosage for SPRAVATO

Induction Phase	Weeks 1 to 4: Administer twice per week Day 1 starting dose: 56 mg Subsequent doses: 56 mg or 84 mg
Maintenance Phase	Weeks 5 to 8: Administer once weekly 56 mg or 84 mg Week 9 and after: Administer every 2 weeks or once weekly* 56 mg or 84 mg

*Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

Administration Instructions
SPRAVATO is for nasal use only. The nasal spray device delivers a total of 28 mg of esketamine. **Each nasal spray device delivers two sprays containing a total of 28 mg esketamine.** To prevent loss of medication, do not prime the device before use. Use 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device.

Post-Administration Observation
During and after SPRAVATO administration at each treatment session, observe the patient for at least 2 hours until the patient is safe to leave. Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities,

such as driving a motor vehicle or operating machinery, until the next day after a restful sleep.

Missed Treatment Session(s)
If a patient misses treatment sessions and there is worsening of depression symptoms, per clinical judgment, consider returning to the patient's previous dosing schedule (i.e., every two weeks to once weekly, weekly to twice weekly; see Table 1).

CONTRAINDICATIONS
Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation.

History of intracerebral hemorrhage

Hypersensitivity to esketamine, ketamine, or any of the excipients.

WARNINGS AND PRECAUTIONS
Sedation
In clinical trials, 49% to 61% of SPRAVATO-treated patients developed sedation based on the Modified Observer's Alertness/Sedation scale (MOAA/s) and 0.3% of SPRAVATO-treated patients experienced loss of consciousness (MOAA/s score of 0).

Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

Dissociation
The most common psychological effects of SPRAVATO were dissociative or perceptual changes (distortion of time, space, illusions), derealization and depersonalization. Sixty-one (61%) to 75% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician Administered Dissociative Symptoms Scale. Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. In clinical trials, dissociation was transient and occurred on the day of dosing.

Abuse and Misuse
SPRAVATO contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient's risk for abuse or misuse prior to prescribing SPRAVATO and monitor all patients receiving SPRAVATO for the development of these behaviors or conditions, including drug-seeking

behavior, while on therapy. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of SPRAVATO. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence.

SPRAVATO Risk Evaluation and Mitigation Strategy (REMS)
SPRAVATO is available only through a restricted program under a REMS called the SPRAVATO REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse.

The following information is from www.SPRAVATOrems.com
How does my <u>Healthcare Setting</u> become certified in the SPRAVATO REMS?
Step 1: Designate an Authorized Representative to oversee implementation and compliance with the REMS requirements

Step 2: Review the following materials: a) SPRAVATO REMS Fact Sheet; b) SPRAVATO Prescribing Information; c) SPRAVATO Medication Guide; d) SPRAVATO Instructions for Use

Step 3: Complete and submit (online or by fax) the SPRAVATO REMS Healthcare Setting Enrollment Form to the REMS

How does my <u>Pharmacy</u> become certified in the SPRAVATO REMS?
Step 1: Designate an Authorized Representative to oversee implementation and compliance of the SPRAVATO REMS requirements

Step 2: Review the following materials: a) SPRAVATO REMS Fact Sheet; b) SPRAVATO Prescribing Information; c) SPRAVATO Medication Guide; d) SPRAVATO Instructions for Use

Step 3: Complete and submit (online or by fax) the SPRAVATO REMS Pharmacy Enrollment Form to the REMS

How do I (<u>Patients</u>) enroll in the SPRAVATO REMS? These are the steps to take in partnership with your healthcare provider:
Step 1: Read the SPRAVATO Medication Guide and Instructions for Use. Your healthcare provider will review specific risk and safety information of SPRAVATO with you and describe how to use the product.

Step 2: Ask your healthcare provider any questions you have about taking SPRAVATO and about the SPRAVATO REMS.

Step 3: Make sure you understand:
How to enroll and take part in the SPRAVATO REMS
The benefits and risks of SPRAVATO
That each time you receive SPRAVATO

You will need to use SPRAVATO nasal spray yourself under direct observation of a healthcare provider in a healthcare setting, such as a doctor's office, clinic, or hospital

You will be monitored by a healthcare provider for at least 2 hours; the healthcare provider will then decide when you are ready to leave the healthcare setting.

After treatment with SPRAVATO, **do not** drive, operate heavy machinery, or do anything where you need to be completely alert until the next day following a restful sleep**.**

Step 4: Together with your healthcare provider complete and sign the SPRAVATO REMS Patient Enrollment Form. Your healthcare provider will fill out most of the enrollment form for you and will send the form to SPRAVATO REMS.

Suicidal Thoughts and Behaviors in Adolescents and Young Adults
In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients (SPRAVATO is not approved in pediatric patients), the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD).

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Increase in Blood Pressure
SPRAVATO causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after SPRAVATO administration and last approximately 4 hours.

Approximately 8% to 17% of SPRAVATO-treated patients and 1% to 3% of placebo-treated patients experienced an increase of more than 40 mmHg

in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. The mean placebo-adjusted increases in systolic and diastolic blood pressure over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients receiving SPRAVATO plus oral antidepressants.

SPRAVATO is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage). Before prescribing SPRAVATO, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO outweigh its risks.
Assess BP prior to administration of SPRAVATO. In patients whose BP is elevated prior to SPRAVATO administration (as a general guide: >140/90 mmHg) a decision to delay SPRAVATO therapy should take into account the balance of benefit and risk in individual patients.

BP should be monitored for at least 2 hours after SPRAVATO administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants or monoamine oxidase inhibitors (MAOIs).

In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Cognitive Impairment
Short-Term Cognitive Impairment
In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment
Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of SPRAVATO nasal spray on

cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO have not been evaluated beyond one year.

Impaired Ability to Drive and Operate Machinery
Two placebo-controlled studies were conducted to assess the effects of SPRAVATO on the ability to drive. The effects of SPRAVATO 84 mg were comparable to placebo at 6 hours and 18 hours post-dose. However, two SPRAVATO-treated subjects in one of the studies discontinued the driving test at 8 hours post-dose because of SPRAVATO-related adverse reactions.

Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO.

Ulcerative or Interstitial Cystitis
Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which included treatment for up to a year.

Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO, and refer to an appropriate healthcare provider as clinically warranted.

Embryo-fetal Toxicity
Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO *in utero*. Advise women of reproductive potential to consider pregnancy planning and prevention.

ADVERSE REACTIONS
The most commonly observed adverse reactions in TRD patients treated with SPRAVATO plus oral AD (incidence $\geq$ 5% and at least twice that of placebo nasal spray plus oral AD) were **dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.**

Adverse reactions occurring in $\geq$ 2% of TRD patients treated with SPRAVATO + oral AD at any dose and at a greater rate than patients treated with placebo nasal spray + oral AD

	SPRAVATO + oral AD (n = 346)	**Placebo + oral AD (n = 222)**
Cardiac disorders		
Tachycardia	6 (2%)	1 (0.5%)
Ear and labyrinth disorders		
Vertigo	**78 (23%)**	**6 (3%)**
Gastrointestinal disorders		
Constipation	11 (3%)	3 (1%)
Diarrhea	23 (7%)	13 (6%)
Dry mouth	19 (5%)	7 (3%)
Nausea	**98 (28%)**	**19 (9%)**
Vomiting	**32 (9%)**	**4 (2%)**
General disorders and administration site conditions		
Feeling abnormal	12 (3%)	0 (0%)
Feeling drunk	**19 (5%)**	**1 (0.5%)**
Investigations		
Blood pressure increased	**36 (10%)**	**6 (3%)**
Nervous system disorders		
Dizziness	**101 (29%)**	**17 (8%)**
Dysarthria	15 (4%)	0 (0%)
Dysgeusia	66 (19%)	30 (14%)
Headache	70 (20%)	38 (17%)
Hypoesthesia	**63 (18%)**	**5 (2%)**
Lethargy	**37 (11%)**	**12 (5%)**
Mental impairment	11 (3%)	2 (1%)
Sedation	**79 (23%)**	**21 (9%)**
Tremor	12 (3%)	2 (1%)
Psychiatric disorders		
Anxiety	**45 (13%)**	**14 (6%)**
Dissociation	**142 (41%)**	**21 (9%)**
Euphoric mood	15 (4%)	2 (1%)
Insomnia	29 (8%)	16 (7%)
Renal and urinary disorders		
Pollakiuria	11 (3%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders		
Nasal discomfort	23 (7%)	11 (5%)
Oropharyngeal pain	9 (3%)	5 (2%)
Throat irritation	23 (7%)	9 (4%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	14 (4%)	5 (2%)

DRUG INTERACTIONS

Central Nervous System Depressants Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation. Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

Psychostimulants
Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafanil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants.

Monoamine Oxidase Inhibitors (MAOIs)
Concomitant use with monoamine oxidase inhibitors (MAOIs) may increase blood pressure. Closely monitor blood pressure with concomitant use of SPRAVATO with MAOIs.

Use in Specific Populations
Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at *https://womensmentalhealth.org/clinical-and-researchprograms/pregnancyregistry/antidepressants/*.

Risk Summary
SPRAVATO is not recommended during pregnancy. There are insufficient data on SPRAVATO use in pregnant women to draw conclusions about any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO *in utero*. There are risks to the mother associated with untreated depression in pregnancy. If a woman becomes pregnant while being treated with SPRAVATO, treatment with esketamine should be discontinued and the patient should be counseled about the potential risk to the fetus.

Lactation
Esketamine is present in human milk. There are no data on the effects of SPRAVATO on the breastfed infant or on milk production. Published studies in juvenile animals report neurotoxicity. Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with SPRAVATO.

Females and Males of Reproductive Potential
Contraception
Based on published animal reproduction studies, SPRAVATO may cause embryo-fetal harm when administered to a pregnant woman. However, it is not clear how these animal findings relate to females of reproductive potential treated with the

recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO.

Pediatric Use
The safety and effectiveness of SPRAVATO in pediatric patients have not been established.

Geriatric Use
Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO, (n =1601), 194 (12%) were 65 years of age and older, and 25 (2%) were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age. The mean esketamine C_{max} and AUC values were higher in elderly patients compared with younger adult patients.

Hepatic Impairment
The mean esketamine AUC and $t_{1/2}$ values were higher in patients with moderate hepatic impairment compared to those with normal hepatic function. SPRAVATO-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended.

CLINICAL STUDIES
TRANSFORM-2 (NCT02418585) is a four-week, randomized, placebo-controlled, double-blind, multicenter, phase 3 trial that compares the effect of treatment with a newly initiated daily oral antidepressant (AD) plus flexible doses of intranasal SPRAVATO versus newly initiated daily oral AD plus intranasal placebo.

The study was conducted in adult patients 18 to < 65 years of age with a DSM-5 diagnosis of **single episode (≥ 2 years)** or **recurrent major depressive disorder without psychotic features**. Inclusion criteria also included an Inventory of Depressive Symptomatology-Clinician rated (IDS-C30) total score ≥ 34 and additional requirements which are listed below in the description of the screening/prospective observational phase.

Exclusion criteria included the following: previous nonresponse of depressive symptoms to esketamine or ketamine in the current MDE; previous nonresponse, in the current MDE, to all four of the oral antidepressant treatment options available for the DB induction phase (duloxetine, escitalopram, sertraline, venlafaxine XR); nonresponse to an adequate course of treatment with ECT in the current MDE; received vagal nerve stimulation or deep brain stimulation in the current MDE; current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar, or related disorders, comorbid obsessive compulsive disorder, intellectual disability, or personality disorder; homicidal ideation/intent; suicidal ideation with some intent to act within six months prior to the

start of the screening/prospective observational phase; history of moderate or severe substance or alcohol use disorder.

TRANSFORM 2 began with a 4 to 7 week screening/prospective observational phase. **Prior to entry into this phase**, **eligible participants were required (1) to have demonstrated documented nonresponse, per the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ) to one to no more than five antidepressant treatments in the current episode of depression and (2) to have been taking a different oral AD medication at or above the minimum therapeutic dose for at least the previous two weeks.** All antidepressant medications continued at this same dose for weeks 1 through 4 of the screening/prospective observation phase with an option to taper the antidepressants over the additional 3 weeks. Non-response was defined as $\leq$ 25% improvement in MADRS total score from week 1 to week 4 and a MADRS total score $\geq$ 28 at weeks 2 and 4.

Non-responders were randomized 1:1 to four weeks of DB treatment with either newly initiated daily oral AD plus flexible doses of intranasal SPRAVATO or newly initiated daily oral AD plus intranasal placebo. Under researchers' supervision, patients self-administered SPRAVATO 56 mg on day 1, then flexible doses of 56 or 84 mg on days 4, 8, 11, or 15, after which the dose remained stable. Two-thirds (66.7%) of patients were taking 84 mg by the end of the DB phase. Based on prior treatment history investigators also started open-label treatment with duloxetine, escitalopram, sertraline, or extended-release venlafaxine following a fixed titration schedule. Thirty-two (32%) of patients received SSRIs while the remaining 68% received SNRIs.

Results

Participants had a median age of 47 years (range 19 to 64 years) and were 62% female, 93% Caucasian, and 5% Black. Approximately 36% of the participants had been treated with 3-5 previous antidepressant medications in the current depressive episode.

The primary efficacy measure was change from baseline (BL) in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at four weeks. The MADRS is a clinician-rated, ten-item scale with a score range of 0 to 60 (higher scores indicate more severe depression). **Compared to placebo nasal spray plus a newly initiated oral AD, SPRAVATO plus a newly initiated oral AD showed statistical superiority on the primary efficacy measure (see Table 1).**

Table 1: Change from BL in MADRS Total Score at Week 4				
Treatment Group	**Number of Patients**	**Mean BL Score (SD)**	**LS Mean (SE) Change from BL to**	**LS Mean Difference (95% CI)***

			end of Week 4	
SPRAVATO (56 mg or 84 mg) + Oral AD**	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (-7.3;-0.6)
Placebo nasal spray + Oral AD	109	37.3 (5.7)	-15.8 (1.3)	

*Difference (SPRAVATO + Oral AD minus Placebo nasal spray + Oral AD) in least-squares mean change from BL

**SPRAVATO + Oral AD was statistically significantly superior to placebo nasal spray + oral AD

SUSTAIN-1 (3003 Trial, NCT 02493868)
Methods/Study Design
Daly et al (2018) conducted a multi-center, double-blind, randomized withdrawal study to assess the efficacy of SPRAVATO + AD compared with an AD + PBO in **delaying relapse of depressive symptoms** in patients with TRD who were in stable remission after an induction and optimization course of SPRAVATO + AD.

Patients either directly entered the study or transferred in from the short-term trials. The study consisted of up to five phases: (1) screening/prospective observational phase (4-7 weeks) and (2) open-label induction phase (4 weeks) for direct-entry patients only; (3) optimization phase (12 weeks; open-label for direct-entry patients and double-blind for transfer-entry patients); (4) maintenance phase (variable duration; double-blind for all patients); (5) follow-up phase (2 weeks). **The study continued until a prespecified number of relapses occurred**.

At the end of the induction phase, both direct-entry and transfer-entry patients who were treatment responders ($\geq$ 50% reduction in MADRS total score from baseline) entered a 12-week optimization phase. During this phase, the oral AD and study drug nasal spray (either SPRAVATO or placebo) remained constant, but the frequency of nasal spray medication was reduced to weekly for the first 4 weeks, then individualized to either once weekly or once every 2 weeks based on patient response.

The maintenance phase began at week 16 (after the induction and optimization phases). Investigators randomized (1:1) SPRAVATO plus oral AD remitters and responders to either continue on SPRAVATO plus AD or to switch to placebo nasal spray plus oral AD. Stable remission was defined as a MADRS score $\leq$ 12 for at least three of the last four weeks prior to randomization. Stable response was defined as $\geq$ 50% decrease in MADRS total score from baseline in each of the last two weeks prior to randomization, but not meeting criteria for stable remission. The primary efficacy endpoint was time to relapse among stable remitters during the maintenance phase. Relapse was defined as MADRS total score $\geq$ 22 for 2 consecutive assessments separated by 5 to 15 days or hospitalization for worsening depression, suicide attempt, suicide prevention or completed suicide, or any other

clinically relevant event suggestive of relapse (as assessed by a Relapse Adjudication Committee).

Study Population
Inclusion criteria: male or female 18 to 64 years of age, inclusive, with recurrent or single episode (≥ 2 years) MDD (per DSM-5 criteria) without psychotic features, as established using clinical assessment, and confirmed by the Mini-International Neuropsychiatric Interview (MINI); having an IDS-C30 total score of ≥34 and total score ≥ 28 on the MADRS (remote, independent rater), consistent with moderate-to-severe depression; and having TRD, defined as nonresponse (≤25% improvement) to ≥2 but ≤5 oral antidepressant treatments taken at adequate dosage and duration for the current episode of depression assessed by the Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire (MGH-ATRQ).

Exclusion criteria: Previous nonresponse of depressive symptoms to ESK or ketamine in the current major depressive episode (MDE), to all 4 of the oral antidepressant treatment options available for the double-blind induction phase (duloxetine, escitalopram, sertraline, and venlafaxine XR) in the current MDE, or nonresponse to an adequate course of treatment with electroconvulsive therapy (ECT) in the current MDE; received vagal nerve stimulation (VNS) or deep brain stimulation (DBS) in the current episode of depression; had a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders (confirmed by the MINI), comorbid obsessive compulsive disorder (OCD), intellectual disability, or personality disorder; having homicidal ideation/intent (per investigator's clinical judgment), or suicidal ideation with some intent to act within 6 months prior to the start of the screening/prospective observational phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS); or history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria.

Results
Baseline Characteristics
Of the 705 patients who enrolled, 437 entered directly into the study and the other patients transferred from one of two short-term ESK studies (fixed dose, n=150; flexible dose, n=118). The treatment groups of stable remitters (n=176) and stable responders (n=121) were comparable based on demographic and clinical characteristics. For all enrolled patients at baseline of the induction phase, the mean age was 46.1 years, 64.8% were female, 90.1% were white and the mean age when diagnosed with MDD was 32.7 years.

Efficacy
Primary Endpoint: **Among stable remitters, 26.7% of patients in the ESK+AD group and 45.3% of patients in the AD+PBO group experienced a relapse event during the maintenance phase.** Stable remitters in the ESK + AD group were 51% less likely to relapse versus those in the AD + PBO group. The median time to relapse (95% CI) was not estimable (NE) for the ESK+AD group as the 50% relapse rate was not reached based on Kaplan–Meier estimates. The median time to

relapse was 273.0 (97.0; NE) days for the AD+PBO group (Figure: Kaplan-Meier Estimates of Patients Who Remained Relapse-Free - Stable Remitters).

Safety

No new safety concerns were observed in this long-term study with repeated weekly or every other weekly dosing of SPRAVATO + AD. The majority of adverse events (AEs) were mild to moderate, observed post dose on dosing days, and generally resolved in the same day (Table: Adverse Events Reported ≥10% in Either Treatment Group During Maintenance Phase).

Event, n (%)	ESK + AD n = 152	AD + PBO n = 145
Dysgeusia	41 (27.0)	10 (6.9)
Vertigo	38 (25.0)	8 (5.5)
Dissociation	35 (23.0)	0
Somnolence	32 (21.1)	3 (2.1)
Dizziness	31 (20.4)	7 (4.8)
Headache	27 (17.8)	14 (9.7)
Nausea	25 (16.4)	1 (0.7)
Vision blurred	24 (15.8)	1 (0.7)
Hypoesthesia oral	20 (13.2)	0

INTRANASAL KETAMINE

Lapidus et al., 2014

In a randomized, double-blind, cross-over, proof of concept trial, Lapidus et al. studied intranasal ketamine in adults (age 21-65) with depression. Participants had to have failed at least one prior antidepressant (AD) trial in the current episode and were allowed to continue stable doses of psychotropics (including AD) throughout the study. Inclusion criteria included a diagnosis of Major Depressive Disorder (MDD), chronic or recurrent, without psychotic features and a baseline score $\geq$ 30 on the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C) Exclusion criteria included the following: unstable medical/neurological condition, axis I disorder other than MDD, high risk of suicide, substance abuse/dependence in past 6 months, psychotic disorder, bipolar disorder, developmental disorder, lifetime abuse/dependence on ketamine/phencyclidine.

The study consisted of two seven-day treatment periods; treatment periods were at least seven days apart. To progress from the first to the second treatment period, participants had to have an IDS-C score ≥ 24. An anesthesiologist in a clinical research unit provided the 20 minute administration of either 50 mg of racemic ketamine hydrochloride or placebo (0.9% saline solution). Study drug or placebo was provided in identical syringes, containing clear solutions of either 100 mg/ml ketamine in 0.9% saline or saline alone. An LMA MADgic mucosal atomization device (LMA North America, Inc., San Diego, CA) was used to provide 5 intranasal applications of solution (volume 100 µl), separated by five minutes. Each of five ketamine applications provided 10 mg of study drug.

Vital signs (heart rate, blood pressure, respiration, and pulse oximetry) were continuously monitored for at least four hours in the research unit following treatment. In the original protocol, participants remained in the research unit overnight but after safety was shown, the protocol was changed to allow for discharge four hours after treatment with outpatient follow-up.

The primary outcome was change in the Montgomery-Asberg Depression Rating Scale (MADRS) at 24 hours following intervention. In each treatment period, assessments occurred at +40 min, +120 min, +240 min, +24 h, + 48 h, +72 h, and +7 days following treatment administration. Secondary outcomes included change in the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) and Hamilton Anxiety Rating Scale (HAM-A) and the proportion of participants meeting response (≥ 50% decrease in MADRS from baseline) or remission (MADRS ≤ 9) criteria.

Safety and tolerability were evaluated using the following instruments: Brief Psychiatric Rating Scale-Positive sub-scale (BPRS+), Clinician-Administered Dissociative States Scale (CADSS), mood item of the Young Mania Rating Scale (YMRS), Systematic Assessment for Treatment Emergent Effects (SAFTEE). Clinically significant changes were defined as systolic or diastolic blood pressure > 180/100 mmHg or heart rate > 110 beats/minute. Management of adverse effects was provided per protocol or as believed necessary by the treating anesthesiologist.

Twenty individuals qualified for the study and were randomized to one of two treatment orders: ketamine-placebo or placebo-ketamine. Two participants withdrew consent and did not participate in both treatment periods. Thus, 18 patients completed both treatment periods and were included in the modified intent to treat (mITT) sample.

Table One summarizes demographic and clinical characteristics of the study participants.

Characteristic	**Value**
Participants treated, n (%)	20 (100)
Gender (M/F)	10/10
Age at enrollment (yrs)	48.0 $\pm$12.8
Race (%)	
Caucasian	18/20 (90)
Asian	1/20 (5)
Black	0/20 (0)
Other	1/20 (5)
Hispanic (%)	3/20 (15)
Married (%)	6/20 (30)
Employed (%)	10/20 (50)
Age of Onset	21.4 $\pm$12.0
Illness Duration in Years	27.4 $\pm$ 13.7
Length of Current Episode in Years	15.2 $\pm$17.4
Failed Antidepressant Medications	4.1 $\pm$ 3.9
History of ECT (%)	4/20 (20)

History of Psychotherapy (%)	17/19 (89)
History of Suicide Attempts (%)	2/20 (10)
Past Substance Use Disorder (%)	3/20 (15)
Current Anxiety Disorder (%)	4/20 (20)
Melancholic (%)	9/20 (45)
Atypical (%)	2/20 (10)
Baseline IDS-C (Screen)	**42.7 ± 8.5**

Results Compared to placebo, ketamine administration was associated with significant improvement of depressive symptoms at the 24 hour post-intervention time point. The estimated mean difference in MADRS score was 7.6 ± 3.7 (95% CI: 3.9-11.3). Response was defined as a 50% drop in MADRS score. **Twenty-four hours after ketamine administration, 8/18 (44%) of participants responded; 24 hours after placebo administration, 1/18 (6%) responded. Improvement in depressive symptoms was not sustained and there was no significant difference at 72 hours or seven days.** With regard to secondary outcomes, ketamine administration was associated with significant improvement on the QIDS-SR and HAM-A at the 24-hour time point. Mean difference in QIDS-SR was 3.0 ± 2.4 (95% CI: 1.1-4.9). Mean difference in HAM-A was 4.5 ± 3.2 (95% CI: 1.4-7.6).

Intranasal ketamine was associated with small increases on measures of psychosis (BPRS+) and dissociation (CADSS). No relationship was found between antidepressant response and ketamine associated changes in dissociative or psychotomimetic symptoms. Four participants experienced treatment-emergent increases in systolic blood-pressure > 130 mm Hg following ketamine compared to three following placebo. No patients had a diastolic blood pressure > 100 mm Hg. All hemodynamic changes resolved four hours post infusion and there was no association between antidepressant response and hemodynamic changes. The most common adverse events related to ketamine administration were feeling strange/unreal, poor memory, weakness/fatigue. **There were no serious adverse events and most resolved within four hours.**

CONCLUSION

SPRAVATO's approval has been a long-awaited event in the pharmacotherapy of depression. It is exciting to have an antidepressant agent that works fast and may improve suicidal ideation (Canuso et al., 2018). However, its use has significant downsides including lack of long-term effectiveness and safety data, the potential for the development of ketamine use disorder, and cost. As described above, Lapidus et al. (2014) studied intranasal racemic ketamine in adults with depression. The acquisition cost of ketamine solution would undoubtedly be less than that of SPRAVATO but the study only lasted seven days and compounding/administering the final product outside of a research setting would be problematic.

RECOMMENDATION

SPRAVATO should be added to the formulary with restrictions.

References

SPRAVATO (esketamine) nasal spray, prescribing information. 2019 Janssen Pharmaceutical Companies. Revised: 03/2019

Esketamine—Summary of Short-Term Trials in Treatment-Resistant Depression. Obtained from Janssen, Medical Information and Services (Inquiry #01354737) on March 14, 2019.

Esketamine—Summary of Long-Term Trials in Treatment-Resistant Depression. Obtained from Janssen, Medical Information and Services (Inquiry #01354737) on March 14, 2019.

Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. *Am J Psychiatry* 2018;175: 620-630.

Lapidus K, Levitch C, Perez A, et al. A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder. *Biol Psychiatry*. 2014 December 15; 76 (12): 970-976.

Esketamine.https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM631430.pdf

Catherine Hall, PharmD, BCPP, BCACP
Clinical Pharmacist, San Antonio State Hospital
April 5, 2019