HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on January 31, 2020 in Room 125 - ASH Building 552. The meeting was called to order by Dr. Baemayr, on behalf of Dr. Messer, Chair at 9:34 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Angela Babin, RPh	Present	Kenda Pittman, PharmD	Present
Jean Baemayr, PharmD- Secretary	Present	Rishi Sawhney, MD	Present
John Bennett, M.D.	Present	Glenn Shipley, DO	Present
Bonnie Burroughs, RPh	Absent	Ashton Wickramasinghe, MD	Present
Barbara Carroll, RN	Absent	Tim Bray (non-voting)	Absent
German Corso, MD	Present	Brad Fitzwater, M.D. (non-voting)	Present
Ramona Gaston-McNutt, RN	Absent	Connie Horton, RNP (non-voting)	Absent
Catherine Hall, PharmD	Present	Raul Luna, RN, MSN (non-voting)	Absent
Jeanna Heidel, PharmD	Phone	Mike Maples (non-voting)	Absent
Jeffery Matthews, MD	Present	Nina Muse, M.D. (non-voting)	Absent
Mark Messer, DO- Chair	Phone	Peggy Perry (non-voting)	Absent
David Moron, MD	Present	Rachel Samsel, (non-voting)	Absent

Guests Present**:** Patricia Corrigan-Strickland, RPh, Integral Care; Rania Kattura, PharmD, Austin State Hospital; Lisa Mican, PharmD, Austin State Hospital; Brittany Parmentier, PharmD, UT Health East Texas; Ryan Shaw, UT Pharmacist Intern, San Antonio State Hospital.

Introduction and Other Information

Two new committee members were introduced:

- Angela Babin, RPh, Director of Pharmacy Services, The Harris Center for Mental Health and IDD.
- German Corso, MD, Medical Director, Tropical Texas Behavioral Health, Harlingen Clinic
- Dr. Bennett has been reappointed for another term.

Annual Conflict of Interest Declaration

A signed disclosure form was received from each committee member present. None of the forms reviewed indicated any issues with conflict of interest. One declaration from a member who was not present at the meeting is pending.

Review of Minutes of October 25, 2019

The approval of the minutes from the October meeting is pended until the next meeting.

Unfinished Business

TAC Title 25, Part 1, Chapter 415, Subchapter C (April 2017)

Drafts of the TAC and selection to the committee letter, with revisions recommended by the workgroup and by the legal department were reviewed. A clarification of wording to ensure inclusion of the HHSC facilities that treat substance use is being sought. Once clarification is received, the draft will be sent to committee members for an email vote.

Psychotropic Medication Utilization Parameters for Adults (August 2019)

The workgroup has not yet been formed. The committee discussed the workload required to develop such a document and determined that starting with a review of available information that is already developed and routinely updated by other entities would be a reasonable starting point.

On a motion by Ms. Babin, seconded by Dr. Corso, this item will be removed from the agenda. Another item, "Review of Available Resources" will be added to the agenda.

OP 3-1 Anti-androgen Therapy for Aggression (October 2019)

The document with revisions as recommended at the October PEFC meeting was reviewed and approved by the legal department. The revised OP was discussed at the System Medical Executive Committee meeting on January 9, 2020 and approved at the State Hospital Governing Body meeting on January 16, 2020.

The next scheduled review for this policy will be in January 2023.

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.

ADR: lithium toxicity

A 67-year-old Caucasian male was admitted to a state hospital on 8/2 with a diagnosis of bipolar disorder, presenting with mania and psychosis. He was started on risperidone 1 mg twice daily upon admission. Baseline labs drawn on 8/5 were largely within normal limits (wnl), with serum creatinine (SCr) 0.84 mg/dl. Calculated creatinine clearance (CrCl) was 93 ml/min using actual body weight. Lithium 300 mg twice daily was initiated on 8/14. A trough lithium level of 0.32 mmol/l was drawn one week later at 7:50 am; the dose was titrated upwards to lithium 450 mg twice daily on 8/21. On 8/23, lithium 450 mg twice daily was discontinued and lithium ER 900 mg at bedtime was initiated. A lithium level of 0.64 mmol/l was drawn on 8/28 at 7:48 am. The lithium ER dose was increased to 1200 mg at bedtime on 8/29. A lithium level of 1.41 mmol/L was drawn 9/9 at 7:18 am. Per documentation, the patient was displaying no signs of adverse effects related to lithium, notes indicate "No tremor, GI upset, diarrhea, n/v." The dose of lithium ER was decreased to 900 mg at bedtime on that day. On 9/16, there was documentation of emesis twice, patient-reported complaints of upset stomach, and the patient was noted to be shaking, but denied pain, headache, or dizziness. Vitals checked at 3:55 am showed elevated blood pressure 171/75 (recheck 154/74), otherwise wnl (pulse 67, temperature 98.1, respiratory rate 16, O2 saturation 95%). Several labs were ordered to evaluate, including lithium level, which was drawn at 12:30 pm. A critical lithium level returned at 2.63 mmol/L along with an elevated blood urea nitrogen (BUN) of 57 mg/dL, SCr 1.89 mg/dL, estimated glomerular filtration rate (GFR) 36ml/min, calculated CrCL 45 ml/min using actual body weight, and an anion gap of 6 mmol/L. Ammonia and thyroid levels returned wnl. The patient to be transferred to a local medical hospital and was diagnosed with lithium toxicity. Lithium was discontinued, and he remained at the local hospital for one week. Per records from the hospitalization, the patient was also diagnosed with cellulitis and received a prescription for sulfamethoxazole/trimethoprim. Follow up lithium levels obtained on 9/27/19 indicated a level <0.25 mmol/L.

The patient showed no adverse effects with the lithium 1200 mg dosage that was associated with a lithium level of 1.41 mmol/L. Lithium toxicity can often present in patients who suffer a reduction in renal function, which coincides with this patient's increased SCr from a baseline of 0.84 to 1.89 (CrCl of 93 to 45 ml/min).

Dehydration can also exacerbate lithium toxicity and this patient had two instances of emesis the day of this reaction. Dehydration and compromised renal function impair the ability to excrete lithium and can exacerbate lithium toxicity.

ADR: paliperidone/elevated prolactin level

A 44-year-old African American female with a past history of schizophrenia, mild intellectual or developmental disability, hypertension, and diabetes mellitus II was admitted to a state hospital on 7/19. She was noted to be calm and cooperative at admission with significant negative symptoms. Her affect was blunted, she demonstrated significant thought blocking, and had delayed thought processing with a few delusional thoughts present. She reported no history of illicit drug or alcohol abuse. Upon admission, her triglycerides were elevated at 275 mg/dl, and all other labs were unremarkable.

Prior to admission she was prescribed an unknown antipsychotic and antidepressant that she was noncompliant with and was not using upon admission. No psychiatric medications were ordered by admitting physician. The patient stated that she had been on haloperidol and trazodone, and her records also mentioned risperidone and paliperidone of which she stated "the shots hurt" indicating she may have been on paliperidone or risperidone long-acting injectable (LAI). On 7/22, trazodone 50 mg at bedtime was ordered for psychosis due to her willingness to take a medication she had tried before. She stated that haloperidol made her sneeze in the past and she didn't like it, but trazodone helped with the voices and helped her sleep. On 7/29 she was started on oral paliperidone 6 mg in the morning for psychosis due to continued psychotic symptoms and poor behavior over the previous weekend. On 8/7 her paliperidone dose was increased to 9 mg due to continued psychosis and several disruptive, aggressive events requiring restraint. On 8/13 paliperidone was increased to 12 mg in the morning for psychosis due to her tolerating the medication well and reports of some improvement. On 8/29 trazodone was increased to 100 mg at bedtime due to reported difficulty sleeping. From this point in time forwards, the patients sleep improved and her psychosis was gradually improving as well, with no reported adverse effects. On 10/2 she requested a switch to zolpidem at night time as she was not getting as much sleep as she wanted, and zolpidem had worked for her in the past. Zolpidem 2.5 mg at bedtime was started and a trazodone taper was initiated. The patient had no further behavioral issues or medication problems. A prolactin level was ordered after she mentioned to staff that she had not had her period in September or October. Prolactin returned highly elevated at 97.9 ng/ml indicating hyperprolactinemia-induced amenorrhea. The prolactin elevation was most likely related to the use of paliperidone which was maxed out in dose to 12 mg on 8/13, coinciding with the first occurrence of amenorrhea in September. The provider began tapering off paliperidone and alternative antipsychotic options with lower risk of hyperprolactinemia (olanzapine, quetiapine, and clozapine) were discussed with

patient. She agreed to a begin a quetiapine titration to a dose of 800 mg beginning on 11/6. The paliperidone order was set to expire on 11/14.

Antipsychotics with higher affinity for dopamine receptors present with higher risk of prolactin elevations in men and women. Among second generation antipsychotics, paliperidone and risperidone, are the most strongly associated with prolactin elevations (Clinical Therapeutics. 2000;22(9):1085). Paliperidone elevates prolactin levels via dopamine D2 receptor antagonism, and this elevation remains during chronic administration. Hyperprolactinemia may suppress hypothalamic gonadotropin-releasing hormone (GnRH), resulting in reduced pituitary gonadotrophin secretion, which in turn, may inhibit reproductive function by impairing gonadal steroidogenesis (Clinical Endocrinology Oxf. 1976;5(3):273). Antipsychotic-induced prolactin elevation levels of 25 to 100 ng/mL have been associated with sexual dysfunction, gynecomastia, and menstrual disturbances (Pharmacotherapy. 2009 Jan;29(1):64-73). Per HHSC antipsychotic monitoring guidelines, a baseline prolactin level is not indicated for patients and one was not drawn in this case. A serum prolactin level draw is indicated when symptoms are present, especially if they are prescribed paliperidone or risperidone, antipsychotic agents with higher affinity for dopamine receptors and are higher risk for prolactin elevation (American Journal of Psychiatry. 2004;161(8):1334). When patients currently on second generation antipsychotics (SGA) present with symptoms of hyperprolactinemia (sexual dysfunction, galactorrhea, amenorrhea) along with the presence of elevated prolactin levels >20 ng/dl, the recommendation is to discontinue the offending medication, in this instance paliperidone was tapered off, and then initiate another agent with lower incidence of prolactin elevation, such as olanzapine or quetiapine (Psychosomatics. 2014 Jan-Feb;55(1):29-36). Cessation of oral antipsychotics typically results in normalization of prolactin within 2–3 weeks; however, prolactin can remain above pre-treatment values for 6 months or longer after discontinuation of some LAIs (Psychopharmacology 2017; 234:3279–3297). In cases where changing antipsychotics is not feasible or results in failure of therapy, the addition of prolactin lowering therapy like aripiprazole can be initiated (PLoS One. 2015;10(10): e0139717). Given the available data on prolactin elevation with paliperidone and the presence of amenorrhea, it is highly likely that paliperidone was the offending agent in this case. The patient has not yet resumed menstruation according to documentation as of 11/12.

ADR: Severe lithium-induced hypothyroidism

A 55-year-old female with a history of hypothyroidism as well as lithium-induced hypothyroidism dating back to at least 2011 was recently discharged from a state psychiatric hospital in late August. She was stabilized on both lithium and levothyroxine. The last lithium level and thyroid-stimulation hormone (TSH) levels just prior to discharge were lithium 0.82 mmol/l and TSH 0.4 mU/L. Discharge medications were aripiprazole 15 mg twice daily (once daily dosing was reported to

cause headaches), risperidone 4 mg at bedtime, lithium 600 mg in the morning and 750 mg at bedtime, melatonin 6 mg at bedtime, levothyroxine 150 mcg in the morning, clonazepam 1 mg at bedtime, diphenhydramine 50 mg at bedtime, trazodone 100 mg at bedtime, iron sulfate, and vitamins D3, B12, and C.

She was again admitted to the psychiatric hospital in mid-November. Diagnoses include Schizoaffective disorder, Polysubstance abuse, history of nicotine dependence, hypothyroidism, hyperammonemia, and obesity, with a body mass index (BMI) of 36. She was taken from jail to a private psychiatric facility 8 days before she came to the state psychiatric hospital on this current admission. Of note, levothyroxine was not listed on her medication list available in the external records from the private psychiatric hospital. Results of lab work done at the private facility were: hemoglobin A1c (HbA1c) 6.1%, low-density lipoprotein (LDL) 197 mg/dL, high-density lipoprotein (HDL) 59 mg/dL, and triglycerides 161 mg/dL. On admission she was noted to be disheveled, uncooperative, irritable and labile mood, angry, hitting herself in the head with her hand, hypersexual, disrobing, and banging on the nurse's station window. At the time of admission, she was prescribed haloperidol 15 mg twice daily and lithium 300 mg in the morning and 600 mg in the evening. Levothyroxine was not prescribed. Olanzapine 10 mg twice daily as needed for agitation and benztropine 1 mg twice daily for extrapyramidal symptoms (EPS) were added. Two days after admission levothyroxine 50 mcg daily was added and lithium was discontinued the following day due to discovery of a severely elevated TSH of 267.70 mU/L and low free thyroxine (fT4) < 0.25 ng/dL. Other admission labs were: lithium 0.69 mmol/L, rapid plasma reagin (RPR) nonreactive, complete blood count (CBC) wnl with absolute neutrophil count (ANC) of 3.4 cells/microL, white blood cell count (WBC) 6.2 cells/microL, comprehensive metabolic panel (CMP) wnl except BUN 24 mg/dL, Calcium 10.6 mg/dL, and BUN:Scr 26. After lithium discontinuation, divalproex DR was prescribed for mood stabilization. 13 days after admission TSH was 155.79 mU/L with fT4 0.28 ng/dL on levothyroxine 75 mcg daily. 16 days after admission TSH was 182.06 mU/L with fT4 < 0.25 ng/dL on levothyroxine 125 mcg daily. The following day the levothyroxine dose was increased to 175 mcg daily and 45 days after admission the TSH was normal at 2.20 mU/L followed by another normal TSH of 3.24 mU/L 55 days after admission.

Lithium has been reported to suppress thyroid function in approximately 42% of patients and contribute to overt hypothyroidism in 8-19% of patients. The prevalence of lithium-induced hypothyroidism is also higher in women 14% than men 4.5%. Generally, the changes in thyroid function begin 3-6 weeks after initiation of lithium and can typically be controlled with thyroid medication. This patient has a history of significant hypothyroidism with a past high TSH of 257.84 mU/L in November of 2011 while prescribed lithium. High doses of levothyroxine have been utilized in the past to treat lithium-induced hypothyroidism and she has

been off and on lithium therapy over the years. It is likely nonadherence or lack of consistent prescribing of levothyroxine prior to the current admission contributed to the significant elevation in TSH as her TSH was stable on the prescribed dose of lithium and levothyroxine at the time of her last discharge from the state psychiatric hospital at the end of August and had been treated with lithium since mid-June. It is possible hypothyroidism may have contributed to mood symptoms leading up to admission as well as potential metabolic effects.

New Drug Applications

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

Cefdinir (Omnicef®)- presented by Dr. Mican

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

On a motion by Dr. Pittman, seconded by Dr. Matthews, it was recommended to add cefdinir capsules and oral suspension to the formulary.

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

Clotrimazole-betamethasone dipropionate (Lotrisone®) – presented by Dr. Parmentier.

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

On a motion by Dr. Matthews, seconded by Dr. Bennett, it was recommended to add clotrimazole-betamethasone dipropionate cream to the formulary.

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

Risperidone subcutaneous injection (Perseris®)- presented by Dr. Kattura

Please refer to Appendix C for the monograph that was considered when determining action by the committee. Concerns that were discussed included:

- Oral to subcutaneous dosage conversion difficulty for doses above 4mg/day;
- Nursing time required to accurately prepare the dose for administration;
- Difficulty in assuring the patient will not rub or massage the injection site;
- Difficulty in patient acceptance of a lump at the injection site that slowly resolves as the medication is dispersed;

- Lack of patient assistance programs for continuation of therapy in the community; and
- Potential safety issues of having two long-acting injections with the same generic name but very different methods of administration on the formulary.

On a motion by Dr. Matthews, seconded by Dr. Moron, it was recommended decline to add risperidone subcutaneous injection to the formulary at this time.

Apixaban (Eliquis®)- presented by Mr. Shaw

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

On a motion by Dr. Matthews, seconded by Dr. Hall, it was recommended to add apixaban to the formulary.

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

Hepatitis C Drug Purchases

For the first quarter of fiscal year 2020 (September 2019-November 2019), the following purchases for drugs to treat hepatitis C were made:

State Hospitals: $0

State Supported Living Centers: $0

Quarterly Non-Formulary Drug Justification Report

For the first quarter of fiscal year 2020 (September 2019-November 2019), only the state hospitals reported use of non-formulary agents. The state supported living centers currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top five non-formulary agents, by number of orders, that were prescribed in the state hospitals during the first quarter of fiscal year 2020:

Acetaminophen-caffeine- pyrilamime (Midol Menstrual Complete®)
Apixaban (Eliquis®)- added at today's meeting
Clotrimazole-betamethasone dipropionate (Lotrisone®)- added at today's meeting
Flaxseed oil
Solifenacin (Vesicare®)- added at the October PEFC meeting.

HHSC Psychotropic Medications Consent List Annual Review

The committee reviewed an updated list of psychotropic medications requiring consent.

On a motion by Dr. Bennett, seconded by Dr. Moron, the committee approved the updated version. The revised document will be posted on the PEFC website.

Antipsychotic Adverse Reaction Comparison Table Review

The committee reviewed an updated table comparing adverse reaction potential of antipsychotics. The committee determined that the document needed further review before being approved. It may be brought back to the committee at a later date. This item will also be added to the "Review of Available Resources" discussion at the next meeting.

Drug Formulary Sectional Review

In reviewing the formulary drug listings for blood modifying agents, antidotes/deterrents/poison control agents, and intravenous solutions and additives, Dr. Hall made the following recommendations:

Blood Modifying Agents

Clopidogrel (Plavix) – Reserve Use. *Remove from reserve use status.*

Heparin Infusion, premixed: *Remove infusion from the formulary.*

Protamine Injection: *Remove from the formulary.*

Antidotes/deterrents/poison control agents

Rename table and section "Antidotes"

Acetylcysteine Solution, oral inhalation: *Remove oral solution from the Antidotes table, keep inhalation in respiratory section*.

Deferoxamine (Desferal) Powder for injection: *Remove from the formulary.*

Dimercaprol (B.A.L.) Injection: *Remove from the formulary.*

Leucovorin Injection, Powder for injection, oral tablet: Remove from the formulary.

penicillAMINE (Cuprimine) oral capsule, oral tablet: *Remove from the formulary.*

Physostigmine injection: *Remove from the formulary.*

Protamine injection: *Remove from the formulary*.

Rename the "Chemical Dependency Adjuncts" table the "Substance Use Treatments" table.

Disulfiram (Antabuse) oral tablet: *Remove from Antidotes table, keep in Substance Use Treatments table.*

Naltrexone (ReVia) oral tablet, injection, long-acting - RESERVE USE: *Remove from Antidotes table, keep in Substance Use Treatments table*

Nicotine (Nicoderm, Nicotrol, Nicorette) transdermal patch, chewing gum, as polacrilex: *Remove from Antidotes table, add to Substance Use Treatments table*

Antidiabetic Agents

Insulin, Lispro-Insulin, Lispro Protamine (HumaLOG Mix 75/25, HumaLOG Mix 50/50) Injection: 100 units/mL: *correct listing to Insulin, Lispro protamine suspension-insulin lispro*

Glucose Elevating Agents: *Remove category (all items are also in other categories)*

Intravenous Solutions and Additives: *Change Intravenous to Parenteral*

Intravenous Solutions: *Change Intravenous to Parenteral*

Dextrose 5% with Multiple Electrolytes (Baxter) infusion: *Remove from the formulary*

Ringer's Lactate Solution (Hartmann's Solution) infusion *Remove from the formulary*

Sodium Chloride injection, for admixtures: *add injection, for reconstitution*

Water for Injection, infusion: *remove infusion, add injection, for reconstitution*

Electrolyte Replacement Additives

Sodium Bicarbonate: remove from table, parenteral formulation is not on the formulary

Sodium Lactate infusion, concentrate: remove from the formulary

Zinc Sulfate injection: remove from the formulary

On a motion by Ms. Babin, seconded by Dr. Bennett, the changes recommended above were approved. The formulary will be updated.

Drug Deletions

The committee did not consider deleting any products not already specified in the sectional review.

New Dosage Forms

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

Literature Review: High-dose olanzapine

Dr. Hall presented a review of some clinical trials and case reports that evaluate the use of high dose olanzapine in the treatment of schizophrenia. The committee decided against increasing the formulary's suggested maximum daily dose of 30 mg, noting that Clinicians are able to use daily doses greater than 30 mg if they have obtained approval from their facility's medical director (or designee).

Psychotropic Audit Criteria & Guidelines Review

The committee reviewed revised audit criteria and guidelines for:

Atomoxetine

On a motion by Dr. Bennett, seconded by Dr. Matthews, the new audit criteria and guidelines document was approved as presented. The updated document will be posted to the PEFC website.

Beta-blockers

On a motion by Dr. Matthews, seconded by Ms. Babin, the revised audit criteria and guidelines document was approved as modified with additional input from the committee. The updated document will be posted to the PEFC website.

Clondine, guanfacine

On a motion by Dr. Matthews, seconded by Dr. Sawhney, the revised audit criteria and guidelines document was approved as modified with additional input from the committee. The updated document will be posted to the PEFC website.

Stimulants

On a motion by Dr. Bennett, seconded by Dr. Matthews, the revised audit criteria and guidelines document was approved as presented. The updated document will be posted to the PEFC website.

Issues from the Chief Medical Officer, State Hospital System

Dr. Muse was not available to present a report.

Issues from the Medical Services Coordinator, State Supported Living Centers

Dr. Shipley reported that Dr. Lisia Trickett has been hired as the new SSLC Psychiatric Coordinator.

FDA Drug Safety Communications and Recalls

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

Safety-related Labeling Changes

Bupropion: 8.2 Lactation (Pregnancy and Lactation Labeling Rule (PLLR) Conversion; Additions and/or revisions underlined)

Risk Summary

Data from published literature report the presence of bupropion and its metabolites in human milk. There are no data on the effects of bupropion or its metabolites on milk production. Limited data from post marketing reports have not identified a clear association of adverse reactions in the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WELLBUTRIN and any potential adverse effects on the breastfed child from WELLBUTRIN or from the underlying maternal condition.

Data

In a lactation study of ten women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL/kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Post marketing reports have described seizures in breastfed infants. The relationship of bupropion exposure and these seizures is unclear.

Methylphenidate: 8.2 Lactation *(Pregnancy and Lactation Labeling Rule (PLLR) Conversion; Additions and/or revisions underlined)*

Risk Summary

Limited published literature, based on milk sampling from seven mothers reports that methylphenidate is present in human milk, which resulted in infant doses of

0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RITALIN or RITALIN-SR and any potential adverse effects on the breastfed infant from RITALIN or RITALIN-SR or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

Juvenile Animal Toxicity Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 4 times the MRHD of 60 mg/day given to children on a mg/m2 basis

Lurasidone: 5.6 Metabolic Changes, 5.7 Hyperprolactinemia, 6.1 Clinical Trials Experience, 8.4 Pediatric Use (additions underlined)

Pediatric Patients (6 to 17 years)

In a long-term, open-label study that enrolled pediatric patients with schizophrenia, bipolar depression, or autistic disorder from three short-term, placebo-controlled trials 54% (378/701) received lurasidone for 104 weeks:

- 7 % of patients with a normal baseline fasting glucose experienced a shift to high at endpoint while taking lurasidone.
- Shifts in baseline fasting cholesterol from normal to high at 27% (HDL cholesterol) of patients taking lurasidone. Of patients with normal baseline fasting triglycerides, 12% experienced shifts to high.
- The mean increase in weight from open-label baseline to Week 104 was 5.85 kg. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of children and adolescents by comparisons to age- and sex-matched population standards. A z-score change <0.5 SD is considered not clinically significant. The mean change in z-score from open-label baseline to Week 104 was -0.06 SD for body weight and -0.13 SD for body mass index (BMI), indicating minimal deviation from the normal curve for weight gain.
- The median changes from baseline to endpoint in serum prolactin levels were -0.20 ng/mL (all patients), -0.30 ng/mL (females), and -0.05 ng/mL (males). The proportions of patients with a markedly high prolactin level (greater than or equal to 5 times the upper limit of normal) at any time during open-label treatment were 2% (all patients), 3% (females), and 1% (males).

- Adverse events among females in this trial that are potentially prolactin-related include galactorrhea (0.6%). Among male patients in this study, decreased libido was reported in one patient (0.2%) and there were no reports of impotence, gynecomastia, or galactorrhea.
- The mean change from baseline to Week 104 in serum creatinine was +0.07 mg/dL. In patients with a normal serum creatinine at baseline, 6% experienced a shift to high at endpoint.
- There was one adverse event in this trial that was considered possibly drug-related and has not been reported in adults receiving lurasidone: a 10-year-old male experienced a prolonged, painful erection, consistent with priapism, that led to treatment discontinuation.
- The mean increase in height from open-label baseline to Week 104 was 4.94 cm. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of children and adolescents by comparisons to age- and sex- matched population standards. A z-score change <0.5 SD is considered not clinically significant. The mean change in height z-score from open-label baseline to Week 104 was +0.05 SD, indicating minimal deviation from the normal growth curve.

MedWatch Safety Alerts

Gabapentinoids: The FDA is warning that serious breathing difficulties may occur in patients using gabapentin or pregabalin who have respiratory risk factors. These include the use of opioid pain medicines and other drugs that depress the central nervous system, and conditions such as chronic obstructive pulmonary disease that reduce lung function. The elderly are also at higher risk.

The FDA is requiring new warnings about the risk of respiratory depression to be added to the prescribing information of the gabapentinoids. FDA has also required the drug manufacturers to conduct clinical trials to further evaluate their abuse potential, particularly in combination with opioids, because misuse and abuse of these products together is increasing, and co-use may increase the risk of respiratory depression.

Health care professionals should start gabapentinoids at the lowest dose and monitor patients for symptoms of respiratory depression and sedation when co-prescribing gabapentinoids with an opioid or other central nervous system depressant such as a benzodiazepine.

Clozapine: The FDA is strengthening an existing warning that constipation caused by clozapine can, uncommonly, progress to serious bowel complications. This can lead to hospitalization or even death if constipation is not diagnosed and treated quickly. Health care professionals should:

- Evaluate bowel function before starting a patient on clozapine.

- Avoid co-prescribing clozapine with other anticholinergic medicines that can cause gastrointestinal hypomotility.
- Advise patients frequently of the significant risk of constipation and life-threatening bowel issues and the need to stay hydrated to prevent constipation.
- Question patients about the frequency and quality of their bowel movements throughout treatment.
- Advise patients to contact a health care professional right away if they have difficulty having a bowel movement or passing stools, do not have a bowel movement at least three times a week or less than their normal frequency, or are unable to pass gas.
- Monitor patients for symptoms of potential complications associated with gastrointestinal hypomotility such as nausea, abdominal distension or pain, and vomiting.
- Consider prophylactic laxative treatment when starting clozapine in patients with a history of constipation or bowel obstruction.

Recalls

Alprazolam: Mylan Pharmaceuticals is voluntarily recalling of one lot of alprazolam due to the potential presence of foreign substance. Clinical impact from the foreign substance, if present, is expected to be rare, but the remote risk of infection to a patient cannot be ruled out. To date, Mylan has not received any adverse events related to this lot.

Ranitidine: Novitium is voluntarily recalling all quantities and lots, within expiry, of ranitidine capsules because of potential NDMA amounts above levels established by the FDA. To date, Novitium has not received any reports of adverse events related to use of the product as part of this recall.

Ranitidine: Lannett Company, Inc. is voluntarily recalling all lots within expiry of ranitidine syrup to the consumer level due to levels of NDMA above the levels recently established by the FDA for ranitidine syrup.

Mirtazapine: Aurobindo Pharma USA, Inc. is voluntarily recalling one lot of mirtazapine to the consumer level due to a label error; bottles labeled as mirtazapine 7.5 mg may contain 15 mg tablets.

Levetiracetam Oral Solution: Lannett Company, Inc. is voluntarily recalling two lots of Levetiracetam Oral Solution, 100mg/mL to the consumer level due to contamination with Bacillus subtilis. The Bacillus subtilis was identified during an evaluation of a raw material used to manufacture the product. Lannett has not received any reports of adverse events related to this recall to date.

Lamotrigine: Taro Pharmaceuticals is recalling one lot of Lamotrigine Tablets 100 mg, lot # 331771 (expiration date June 2021) in 100 count bottles, NDC 51672-4131-1 because it was found to have been cross-contaminated with a small amount of enalapril maleate. Taro has not received any product complaints or adverse events related to contamination of this product with enalapril.

News Briefs

The following information was shared with the committee members:

Scan Study Reveals No Association Between Statins And Cognitive Problems

The **New York Times** (11/18, Bakalar) reports, "A large Australian study" encompassing 1,037 older adults and involving MRI brain scans "found no association between cholesterol-lowering statins and memory or thinking problems." The study revealed that "the rate of cognitive decline was the same in those who used statins continuously and those who never took them." In addition, "brain volume changes were the same in statin users and in those who never used the drugs." **Reuters** (11/18, Carroll) reports that "the drugs" also "appeared to protect cognition in patients with heart disease," the study found. The findings were published online in the Journal of the American College of Cardiology.

FDA Grants Breakthrough Therapy Designation For Psilocybin For Treatment Of MDD

Medscape (11/25, Brooks, Subscription Publication) reports the FDA "has granted the Usona Institute breakthrough therapy designation for psilocybin for the treatment of major depressive disorder (MDD)," marking the second time the agency "has granted breakthrough designation for psilocybin, the psychoactive ingredient in 'magic mushrooms.'"

FDA Tests Diabetes Drug Metformin For NDMA

Bloomberg (12/4, Lauerman) reports that on Wednesday, the FDA announced that it "is testing samples of metformin sold in the U.S. for NDMA, and that it will recommend recalls of the medication as appropriate." Metformin is prescribed to many patients with type 2 diabetes, and NDMA has been detected in many "heart and gastric medications" prompting recalls. The article adds that the EMA is also concerned about the possibility of high levels of NDMA in metformin and has instructed companies to test for it.

PPIs May Be Associated With Acute Gastroenteritis In Winter

Healio (12/6, Young) reported, "During the winter months, when the circulation of enteric viruses is at its highest, continuous use of proton pump inhibitors are associated with increased risk for developing acute gastroenteritis," research indicated in a study that involved matching "patients exposed to PPIs during the 2015–2016 winter season (n = 233,596) with patients not exposed to PPIs (n = 626,887)." The findings were published online in JAMA Network Open.

Investigators Release New Data On Experimental Tau Inhibitor

Medscape (12/6, Brooks, Subscription Publication) reported, "New data on the experimental tau inhibitor hydromethylthionine has turned up some unexpected results in a post-hoc analysis, according to its manufacturer," TauRx Therapeutics. The study revealed that "even at the 'control' dose of 8 mg per day, the drug produced concentration-dependent effects on cognitive decline and brain atrophy when used alone or added to symptomatic treatment in patients with mild to moderate Alzheimer's disease." Magnetic resonance imaging was involved in the study. The findings of the 1,162-participant study were published online in the Journal of Alzheimer's Disease.

FDA Approves Lumateperone For Schizophrenia With Boxed Warning

Reuters (12/23, Roy) reports the FDA approved Intra-Cellular Therapies Inc.'s Caplyta (lumateperone) "as a once-daily dose of 42 mg" for the treatment of schizophrenia. The company said it plans to launch the drug later in the first quarter of next year and that it will price the drug closer to launch.

MedPage Today (12/23, Hlavinka) reports that how the drug "functions remains unknown, although it is thought to have a triple mechanism of action that targets serotonin, dopamine, and glutamate neurotransmitter pathways." The FDA approved the drug "with a boxed warning about increased risk of death for elderly patients with dementia-related psychosis." The drug's "label also notes increased risk for cerebrovascular events in this population." MD Magazine (12/23, Campbell) reports that in clinical trials, the most commonly reported side effects "were somnolence/sedation and dry mouth."

Antipsychotics May Cause Increased Risk Of Death Or Cardiopulmonary Arrest In Older Adults

MD Magazine (1/7, Walter) reports researchers "evaluated the risk of death or nonfatal cardiopulmonary arrest in hospitalized adults exposed to antipsychotics at a large academic medical center." Included in the study were "data from 150,948 hospitalizations...with 691 total events – 515 deaths and 176 cardiopulmonary arrests." The study revealed that for patients who were 65 years old and older, "both typical and atypical antipsychotics were associated with increased risk of death or cardiopulmonary arrest." The findings were published online Nov. 19 in the Journal of the American Geriatrics Society.

FDA Approves Diazepam Nasal Spray For Seizure Clusters And Acute Repetitive Seizures

Medscape (1/14, Brooks, Subscription Publication) reports the FDA approved Neurelis' Valtoco (diazepam nasal spray) "for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity such as seizure clusters and acute repetitive seizures that are distinct from a patient's usual seizure pattern." The agency approved the drug for patients with epilepsy who are at least 6 years old.

Open Forum

Several committee members reported having received unsolicited emails from pharmaceutical representatives that appear to have been initiated in response to items posted in the committee minutes. The committee members agreed that such contact is inappropriate and will monitor these communications. If any trends or patterns emerge, the committee will consider seeking consultation with the HHSC legal and/or ethics departments.

Next Meeting Date

The next meeting is scheduled for April 17, 2020.

Adjourn

There being no further business, the meeting was adjourned at 3:10 p.m.

Approved: Mark Messer, D.O.

Mark Messer, D.O., Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

Appendix

- Appendix A – Cefdinir (Omnicef®) monograph
- Appendix B – Clotrimazole-betamethasone dipropionate (Lotrisone®) monograph
- Appendix C – Risperidone subcutaneous (Perseris®) monograph
- Appendix D – Apixaban (Eliquis®) monograph

Appendix A

Cefdinir (Omnicef®)

Classification

Third generation cephalosporin antibiotic

Pharmacology

OMNICEF® (cefdinir) capsules for oral administration contain the active ingredient, cefdinir, an extended-spectrum, semisynthetic cephalosporin. As with other cephalosporins, bactericidal activity of cefdinir results from inhibition of cell wall synthesis. Cefdinir is stable in the presence of some, but not all, β-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins are susceptible to cefdinir; it has enhanced activity against aerobic gram-negative bacteria including E. coli, Klebsiella sp. and P. mirabilis, as well as some anaerobic bacteria. It is also inactive against most strains of *Enterobacter* spp., *Pseudomonas* spp., *Enterococcus* spp., penicillin-resistant streptococci, and methicillin-resistant staphylococci.

Indication -FDA & literature supported non-FDA

Cefdinir is FDA approved for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated bacteria in the following conditions:

Adults and Adolescents

- Community-Acquired Pneumonia & Acute Exacerbations of Chronic Bronchitis caused by *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis* (all including β-lactamase producing strains), and *Streptococcus pneumoniae* (penicillin-susceptible strains only).
- Acute Maxillary Sinusitis caused by *Haemophilus influenza* and *Moraxella catarrhalis* (including β-lactamase producing strains), and *Streptococcus pneumoniae* (penicillin-susceptible strains only).
- Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes*.
- Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes*.

Pediatric Patients

- Acute Bacterial Otitis Media caused by *Haemophilus influenza* and *Moraxella catarrhalis* (including β-lactamase producing strains), and *Streptococcus pneumoniae* (penicillin-susceptible strains only).

Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes*.
Off label alternative use in the management of acute uncomplicated cystitis

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Maximal plasma cefdinir concentrations occur 2 to 4 hours postdose following capsule administration. Suspension bioavailability is 120% relative to the capsule formulation. Absorption not significantly impacted by food.
Distribution	The mean volume of distribution (Vd_{area}) of cefdinir in adult subjects is 0.35 L/kg (± 0.29); in pediatric subjects (age 6 months-12 years), cefdinir Vd_{area} is 0.67 L/kg (± 0.38). 60-70% bound to plasma proteins.
Metabolism	Cefdinir is not appreciably metabolized. Activity is primarily due to parent drug.
Excretion	Cefdinir is eliminated principally via renal excretion with a mean plasma elimination half-life (t½) of 1.7 (± 0.6) hours. Because renal excretion is the predominant pathway of elimination, dosage should be adjusted in patients with markedly compromised renal function or who are undergoing hemodialysis

Dosage/Administration

The total daily dose for all adult and adolescent (13 years of age and older) infections is 600 mg. Once-daily dosing for 10 days is as effective as BID dosing. Once-daily dosing has not been studied in pneumonia or skin infections; therefore, cefdinir capsules should be administered twice daily in these infections. Cefdinir capsules may be taken without regard to meals.

The recommended dosage and duration of treatment of infections in pediatric patients (6 months through 12 years of age) is a total daily dose of 14 mg/kg, up to a maximum of 600 mg per day. Pediatric patients 43 kg or more should receive the maximum dose of 600 mg per day.

See product labeling for additional specific dosage information based on age group and type of infection treated.

Use in Special Population

Patients with renal insufficiency:
Dosage adjustment is recommended in patients with markedly compromised renal function (creatinine clearance < 30 mL/min) as AUC is increased approximately 6-fold.

Hemodialysis:
Dialysis (4 hours duration) removed 63% of cefdinir from the body and reduced apparent elimination t½ from 16 (± 3.5) to 3.2 (± 1.2) hours. Dosage adjustment is recommended

Hepatic Disease:
Because cefdinir is predominantly renally eliminated and not appreciably metabolized, studies in patients with hepatic impairment were not conducted. It is not expected that dosage adjustment will be required in this population.

Contraindication

Cefdinir capsules are contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

Precautions

Careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefdinir, other cephalosporins, penicillins, or other drugs. Cross hypersensitivity among β-lactam antibiotics can occur in up to 10% of patients so caution should be exercised if given to penicillin-sensitive patient.

Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including cefdinir, and may range in severity from mild- to life-threatening. Consider this diagnosis in patients who present with diarrhea after the administration of cefdinir.

Prescribing cefdinir capsules in the absence of a proven or strongly suspected bacterial infection or indication is unlikely to benefit the patient and increases the risk of development of drug-resistant bacteria.

Prolonged treatment may result in the possible emergence and overgrowth of resistant organisms.

Caution should be used when prescribing in patients with history of colitis.

In patients with transient or persistent renal insufficiency (creatinine clearance <30 mL/min), the total daily dose of cefdinir should be reduced.

Adverse Effects

More Common
Gastrointestinal: Diarrhea (8% to 15%)
Genitourinary: Vulvovaginal candidiasis (≤4%), urine abnormality (increased leukocytes: ≤2%), proteinuria (1% to 2%)
Dermatologic: Skin rash (≤3%)

Gastrointestinal: Nausea (≤3%)
Central nervous system: Headache (2%)
Hematologic & oncologic: Lymphocytosis (≤2%)
Other Less Common

Decreased serum bicarbonate (≤1%), glycosuria (≤1%), hyperglycemia (≤1%), hyperphosphatemia (≤1%), increased gamma-glutamyl transferase (≤1%), increased lactate dehydrogenase (≤1%), abdominal pain (≤1%), vomiting (≤1%), occult blood in urine (≤1%), vaginitis (≤1%), eosinophilia (1%), lymphocytopenia (1%), abnormal neutrophils (functional disorder of polymorphonuclear neutrophils: ≤1%), thrombocythemia (≤1%), change in WBC count (≤1%), increased serum alkaline phosphatase (≤1%), increased serum ALT (≤1%), increased urine pH (≤1%), increased urine specific gravity (≤1%)

Cephalosporin class adverse events

Allergic reactions, anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive test for urinary glucose, neutropenia, pancytopenia, and agranulocytosis.

Pseudomembranous colitis symptoms may begin during or after antibiotic treatment.

Several cephalosporins have been implicated in triggering seizures, particularly in

patients with renal impairment when the dosage was not reduced.

Monitoring

Monitor renal function. Observe for signs and symptoms of anaphylaxis during first dose.

Interactions

Antacids (aluminum- or magnesium-containing): Concomitant administration of 300 mg cefdinir capsules with 30 mL Maalox® TC suspension reduces the rate (Cmax) and extent (AUC) of absorption by approximately 40%. Time to reach Cmax is also prolonged by 1 hour. There are no significant effects on cefdinir pharmacokinetics if the antacid is administered 2 hours before or 2 hours after cefdinir. If antacids are required during cefdinir therapy, cefdinir should be taken at least 2 hours before or after the antacid.

Iron supplements and foods fortified with iron: Concomitant administration with iron supplements containing 60 mg of elemental iron (as ferrous sulfate) or vitamins supplemented with 10 mg of elemental iron reduce the extent of absorption by 80% and 31% respectively. Cefdinir should be taken at least 2 hours before or after iron containing supplements. No significant effect with iron-fortified infant formula. Iron fortified foods have not been studied. Reddish stools may occur, particularly in those receiving iron-containing products due to a nonabsorbable complex between cefdinir.

Efficacy

Community-Acquired Pneumonia (CAP)

Cefdinir 300 mg twice daily was compared to Cefaclor 500 mg three times daily (second generation cephalosporin) in adults and adolescents for the treatment of CAP [1]. Clinical cure rates were similar between the two antibiotics, 80% and 79% respectively. Overall eradiation rates were also similar between the two antibiotics, 91% and 92% respectively.

Cefdinir 300 mg twice daily was also compared to amoxicillin/clavulanate 500/125 mg three times daily in adults and adolescents for the treatment of CAP [1]. Clinical cure rates were superior for amoxicillin/clavulanate (89%) compared to cefdinir (80%). Overall eradication rates were similar between the two antibiotics, cefdinir (89%) and amoxicillin/clavulanate (93%).

Initial Treatment Strategies for Outpatients with Community-acquired Pneumonia per 2019 American Thoracic Society & IDSA Treatment Guidelines include recommendations for those with no comorbidities or risk factors for MRSA or Pseudomonas aeruginosa and those with comorbidities [4]. Risk factors include prior respiratory isolation of MRSA or P. aeruginosa or recent hospitalization and receipt of parenteral antibiotics in the last 90 days. Comorbidities include chronic heart, lung, liver or renal disease; diabetes, alcoholism; malignancy; or asplenia. Those with no comorbidities or risk factors, amoxicillin, doxycycline or a macrolide (if local pneumococcal resistance is less than 25%) such as azithromycin or clarithromycin can be considered. Those with comorbidities, combination therapy with amoxicillin/clavulanate or cephalosporin (examples include cefpodixime- 3rd generation or cefuroxime- 2nd generation) AND macrolide or doxycycline OR monotherapy with a respiratory fluoroquinolone (examples include levofloxacin, moxifloxacin or gemifloxacin) can be considered.

Acute Exacerbations of Chronic Bronchitis

CDC antibiotic prescribing guidelines in adults note that antibiotics are not recommended for acute uncomplicated bronchitis regardless of the cough duration. Treatment options generally include symptomatic management with cough

suppressants, antihistamines or decongestants. For those with chronic bronchitis half of acute exacerbations may be due to a bacterial infection [6]. For moderate to severe flares antibiotics may be indicated. Cephalosporins such as cefdinir may be used for uncomplicated flares (age less than 65, FEV1 > 50 of predicted, less than 2 exacerbations per year and no cardiac disease). In addition to antibiotics, use of corticosteroids and inhaled bronchodilators are generally also important aspects of treatment.

Acute Maxillary Sinusitis

CDC antibiotic prescribing guidelines in adults note that 98% of sinusitis cases are viral and antibiotics are not guaranteed to help [5]. **Acute bacterial rhinosinusitis** based on symptoms that are: Severe (>3-4 days), such as a fever ≥39°C (102°F) and purulent nasal discharge or facial pain; persistent (>10 days) without improvement, such as nasal discharge or daytime cough; or worsening (3-4 days) such as worsening or new onset fever, daytime cough, or nasal discharge after initial improvement of a viral upper respiratory infections (URI) lasting 5-6 days. Watchful waiting is encouraged for uncomplicated cases for which reliable follow-up is available. Amoxicillin or amoxicillin/clavulanate is the recommended first-line therapy. Macrolides such as azithromycin are not recommended due to high levels of Streptococcus pneumoniae antibiotic resistance (~40%). For penicillin-allergic patients, doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) may be used as alternative agents.

Pharyngitis/Tonsillitis

Two studies (one in adults and adolescents and the other in pediatric patients) compared cefdinir 600 mg once daily or 300 g twice daily to penicillin 250 mg (or 10 mg/kg) four times daily for 10 days in the treatment of pharyngitis/tonsillitis [1]. Cefdinir once daily or twice daily was superior to penicillin 250 mg four times daily for both eradication of S. pyogenes and clinical cure rate for the adult/adolescent population as well as the pediatric population.

Two studies (one in adults and adolescents and the other in pediatric patients) compared cefdinir 300 mg twice daily for 5 days to penicillin 250 mg (or 10 mg/kg) four times daily for 10 days [1]. Cefdinir twice daily was equivalent to penicillin 250 mg four times daily for both eradication of S. pyogenes and clinical cure rate for the adult/adolescent population as well as the pediatric population.

Uncomplicated Skin and Skin Structure Infections caused by Staphylococcus aureus

Management of skin and soft tissue infections (SSRIs) 2014 IDSA Practice Guidelines include a number of management recommendations [7]. Staphylococcus aureus (S. aureus) and Streptococcus pyogenes are common bacteria found in skin

and soft tissue infections (SSTIs). Impetigo is a common type of skin infection caused by bacteria. Topical therapy such as mupirocin topical ointment applied twice a day for 5 days is a possible treatment option for milder forms of impetigo. Oral therapy is recommended for those with numerous lesions or in outbreaks affecting several people to help decrease transmission. In addition, treatment of deeper level tissue infections such as ecthyma will require oral antibiotics.

Oral therapy for skin infections typically consist of a 7-day regimen with an agent active against S. aureus unless cultures yield streptococci alone, for which a penicillin such as penicillin VK 250-500 mg four times daily or a first-generation cephalosporin such as cephalexin 500 mg four times daily could be considered according to the IDSA guidelines for diagnosis and management of skin and soft tissue infections.

Antibiotics that would cover for methicillin susceptible S. aureus (MSSA) skin infections would be medications such as:

Dicloxacillin 500 mg four times a day (adult dose) OR
Cephalexin 500 mg four times a day (adult dose)

Statewide antibiogram information indicates good susceptibility to these antibiotics. MSSA strains also have good susceptibility to ceftriaxone, another 3rd generation cephalosporin similar to cefdinir.

When methicillin resistant S. aureus (MRSA) is suspected or confirmed antibiotics to consider would include:

Doxycycline 100 mg twice a day (not recommended for children 8 years of age or younger) OR
Trimethoprim/sulfamethoxazole (Bactrim DS) 1-2 double strength tablets twice a day (adult dose)

Statewide antibiogram information indicate good MRSA susceptibility to these antibiotics.

Acute Bacterial Otitis Media (pediatric indication)

CDC pediatric antibiotic prescribing guidelines note that 98% of sinusitis cases are viral and antibiotics are not guaranteed to help. Mild cases with unilateral symptoms in children 6-23 months of age or unilateral or bilateral symptoms in children >2 years may be appropriate for watchful waiting based on shared decision-making. Amoxicillin remains first line therapy for children who have not received amoxicillin within the past 30 days. Amoxicillin/clavulanate is recommended if amoxicillin has been taken within the past 30 days, if concurrent purulent conjunctivitis is present, or if the child has a history of recurrent acute

otitis media unresponsive to amoxicillin. For children with a non-type I hypersensitivity to penicillin (not IgE-mediated reaction): cefdinir, cefuroxime, cefpodoxime, or ceftriaxone may be considered.

Acute Uncomplicated Cystitis (off-label)

Antimicrobial Agents for Empiric Treatment of Acute Uncomplicated Cystitis in Women per the 2010 IDSA and European Society for Microbiology and Infectious Diseases Practice Guidelines recommend β-lactams such as cefdinir (not ampicillin or amoxicillin alone) as well as fluoroquinolones (noting high resistance in some areas) as potential second-line treatment options [2]. The first-generation cephalosporin, cephalexin, is less well studied for UTI. First-line U.S. options based on availability, allergy history and tolerance include nitrofurantoin (avoid if early pyelonephritis suspected), trimethoprim-sulfamethoxazole 160/800 mg (avoid if resistance prevalence exceeds 20% or used for UTI in previous 3 months) or fosfomycin (lower efficacy than some other agents, avoid if early pyelonephritis suspected).

At some state facilities, trimethoprim-sulfamethoxazole resistance to E. coli well exceeds 20% eliminating this first line treatment option. This leaves only nitrofurantoin and fosfomycin as possible first-line empiric treatment options for those facilities. Fluoroquinolones can be used as a second-line option and ofloxacin, ciprofloxacin and levofloxacin are efficacious in a 3 day regimen; however, this class of antibiotics is often discouraged due to emerging resistance patterns and some state facilities also have a fluoroquinolone resistance rate to E. coli well exceeding 20%. Beta-lactam antibiotics (not amoxicillin or ampicillin alone) such as amoxicillin-clavulanate, cefdinir, cefaclor (second generation cephalosporin) and cefpodoxime-proxetil (third generation cephalosporin) in 3-7 day regimens may be appropriate when other first-line options cannot be used. Some state facilities have good susceptibility of E. coli to amoxicillin-clavulanate, 3rd generation cephalosporins as well as some 2nd generation cephalosporins.

Dosage Forms

Cefdinir (Omnicef) 300 mg cap BID
Cefuroxime axetil (Ceftin) 250 mg tab BID
Ceftriaxone (Rocephin) 250 mg injection
Amoxicillin/clavulanate (Augmentin) 500/125 mg tab TID
Penicillin V Potassium (Pen-Vee K) 250 mg tab QID

Special Considerations

Suspension is also available

Summary/Conclusion

Cefdinir is periodically prescribed as a nonformulary medication for bacterial infections. This third generation cephalosporin is available in an oral formulation and has similar clinical cure and eradication rates for community acquired pneumonia as the second generation cephalosporin cefaclor. Community acquired pneumonia eradication rates for amoxicillin/clavulanate were also similar to cefdinir; however, clinical cure rates were superior for amoxicillin/clavulanate (89%) vs cefdinir (80%). Guidelines suggests utility for uncomplicated acute flares of chronic bronchitis. Cefdinir was superior to penicillin for the treatment of pharyngitis with a 10 day course of treatment and similar to penicillin when comparing a 5 day course of cefdinir with a 10 day course of penicillin. Cefdinir is also an option for the treatment of MSSA SSTIs. It can be an alternative treatment option to amoxicillin and amoxicillin/clavulanate in pediatric bacterial otitis media. Guidelines also suggest potential use as a second-line option in the treatment of uncomplicated cystitis. Currently the only second generation cephalosporin on formulary is cefuroxime axetil which is dosed twice daily and the only third generation cephalosporin on formulary is ceftriaxone which is only available in an injectable formulation. The addition of cefdinir would provide an oral third generation cephalosporin treatment option and the ability to dose once daily would provide an advantage over the second generation oral cephalosporin currently on formulary, cefuroxime axetil. Cefdinir is also available as an oral suspension that can be stored at room temperature after reconstitution.

Recommendation

Addition of cefdinir to the formulary is recommended.

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Appendix B
Clotrimazole/betamethasone dipropionate cream (Lotrisone®) Merck Sharp & Dohme Corp.

Classification:
Topical antifungal/ corticosteroid

Pharmacology

Clotrimazole is an azole antifungal agent, which inhibits 14-α-demethylation of lanosterol in fungi by binding to one of the cytochrome P-450 enzymes. This leads to the accumulation of 14-α-methylsterols and reduced concentrations of ergosterol (a sterol essential for a normal fungal cytoplasmic membrane). The methylsterols affect the electron transport system, thereby inhibiting growth of fungi.

Betamethasone dipropionate is a corticosteroid. Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation. The exact mechanism of action for the treatment of tinea pedis, tinea cruris and tinea corporis is unknown.

Indication

Clotrimazole/betamethasone dipropionate is indicated for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis due to *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* in patients who are 17 years and older.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Skin penetration and systemic absorption of clotrimazole and betamethasone dipropionate following topical application has not been studied. The percutaneous absorption of topical corticosteroids is determined by various factors (the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings). Topical corticosteroids can be absorbed from normal intact skin. Inflammation and other disease processes in the skin can increase the percutaneous absorption of topical corticosteroids. Occlusive dressings significantly increase the percutaneous absorption of topical corticosteroids.
Distribution	Once absorbed through the skin, the pharmacokinetics of topical corticosteroids are similar to systemic corticosteroids. Corticosteroids are bound to plasma proteins.
Metabolism	Corticosteroids are metabolized primarily in the liver.
Excretion	Corticosteroids are excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Dosage/Administration

For topical use only; not for oral, ophthalmic, or intravaginal use.

Do not use more than 45 grams per week.

Do not use with occlusive dressings.

Tinea cruris and tinea corporis: Apply a thin layer to the affected skin areas twice a day for 1 week. If a patient shows no clinical improvement after 1 week of use, the diagnosis should be reviewed. Do not use longer than 2 weeks.

Tinea pedis: Massage a sufficient amount of cream into the affected skin areas twice a day for 2 weeks. If a patient shows no clinical improvement after 2 weeks of use, the diagnosis should be reviewed. Do not use longer than 4 weeks.

Use in Special Populations

There are no available data on topical clotrimazole or betamethasone dipropionate use in pregnant women to identify a clotrimazole/betamethasone dipropionate cream associated risk of major birth defects, miscarriage, or adverse maternal and fetal outcomes.

Observational studies suggest an increased risk of low birthweight infants with the use of potent topical corticosteroids during pregnancy. Pregnant women should be advised that clotrimazole/betamethasone dipropionate cream may increase the risk of having a low birthweight infant. Pregnant women should use clotrimazole/betamethasone cream on the smallest area of skin and for shortest duration. There have been no reproduction studies performed in animals or humans with the combination of clotrimazole and betamethasone dipropionate.

There are no data regarding the excretion of clotrimazole or betamethasone dipropionate into breast milk, the effects on the breastfed infant, or the effects on milk production after topical application to women who are breastfeeding. It is possible that topical administration of betamethasone dipropionate could result in sufficient systemic absorption to produce detectable quantities in human milk. The risks and benefits of using clotrimazole/betamethasone while breastfeeding should be considered.

The use of clotrimazole/betamethasone cream is not recommended in patients under the age of 17 years. In open-label trials, some pediatric subjects aged 12-16 years old who used clotrimazole/betamethasone cream demonstrated adrenal suppression as determined by cosyntropin testing. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults for HPA axis suppression when they are treated with topical corticosteroids. They are

also at a greater risk of adrenal insufficiency during and/or after withdrawal of treatment.

Clinical studies of clotrimazole/betamethasone cream did not include sufficient numbers of individuals aged 65 and over to determine whether they respond differently from younger subjects. Greater sensitivity of some older individuals cannot be ruled out. The use of clotrimazole/betamethasone cream under occlusion, such as in diaper dermatitis, is not recommended. Post marketing adverse event reporting for clotrimazole/betamethasone cream in patients aged 65 and above includes reports of skin atrophy and rare reports of skin ulceration. Caution should be used with the use of topical corticosteroids on thinning skin.

Contraindications

No contraindications are listed in manufacturer's labeling.

Precautions

Endocrine system: Systemic absorption of topical corticosteroids may produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency during treatment or after discontinuing treatment. Symptoms of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids during treatment. Because of the potential for systemic corticosteroid effects, patients may need to be periodically evaluated for HPA axis suppression.

Diaper Dermatitis: Clotrimazole/betamethasone is not recommended for use in the treatment of diaper dermatitis.

Ophthalmic Adverse Reactions: Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported in post marketing experience with the use of topical corticosteroid products, including topical betamethasone products. Avoid clotrimazole/betamethasone contact with the eyes. Patients should be advised to report any visual symptoms and consider referral to an ophthalmologist for evaluation.

Adverse Effects

Clinical Trials

Common adverse effects reported in clinical trials included paresthesia in 1.9% of patients. Adverse effects at a frequency of <1% included rash, edema, and secondary infection.

Post Marketing Experience

The following local adverse reactions have been reported in post marketing experience with topical corticosteroids: itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria, capillary fragility (ecchymoses), telangiectasia, and sensitization (local reactions upon repeated application of product).

Ophthalmic adverse reactions of blurred vision, cataracts, glaucoma, increased intraocular pressure, and central serious chorioretinopathy have been reported with the use of topical corticosteroids, including topical betamethasone products.

Adverse reactions reported with clotrimazole include erythema, stinging, blistering, peeling, edema, pruritis, urticaria, and general irritation of the skin.

In the pediatric population, reported adverse events for patients receiving topical corticosteroids included HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension.

Monitoring

Monitor growth in children and adolescents. Monitor for signs and symptoms of HPA axis suppression/adrenal insufficiency. The adrenocorticotropic hormone (ACTH) stimulation test may be used to evaluate for HPA axis suppression. Monitor for signs of skin infection and ocular changes.

Interactions

Corticosteroids may diminish the therapeutic effect of Aldesleukin. Avoid combination.

Corticosteroids may diminish the therapeutic effect of Corticorelin. Monitor therapy.

Corticosteroids may enhance the adverse/toxic effect of Deferasirox, specifically the risk for GI ulceration/irritation or GI bleeding may be increased. Monitor therapy.

Corticosteroids may diminish the therapeutic effect of Hyaluronidase. Larger doses of hyaluronidase may be required. Consider therapy modification.

Corticosteroids may enhance the adverse/toxic effect of Ritodrine. Monitor therapy.

Clotrimazole (topical) may increase the serum concentration of Sirolimus. Monitor therapy.

Clotrimazole (topical) may increase the serum concentration of Tacrolimus. Monitor therapy.

Efficacy

In clinical trials of tinea corporis, tinea cruris, and tinea pedis, subjects treated with clotrimazole/betamethasone showed a better clinical response at the first return visit than subjects treated with clotrimazole cream. The first return visit was 3-5 days for tinea corporis and tinea cruris and 1 week for tinea pedis. Mycological cure rates observed in subjects treated with clotrimazole/betamethasone cream were as good, as, or better than, in those subjects treated with clotrimazole cream. In these same studies, patients treated with clotrimazole/betamethasone cream showed better clinical responses and mycological cure rates when compared with subjects treated with betamethasone dipropionate cream.

Dosage Forms/Cost

Name	Form	Package size	AWP
Clotrimazole	cream	15 gm	$19.90
Betamethasone dipropionate	cream	15 gm	$52.83
Clotrimazole/betamethasone dipropionate (generic)	cream	15 gm	$ 37.49
Clotrimazole/betamethasone dipropionate (generic)	cream	45 gm	$ 73.63
Lotrisone (Brand)	cream	15 gm	$70.20
Lotrisone (Brand)	cream	45 gm	$151.20

Special Considerations

None

Summary/Conclusion

Clotrimazole/betamethasone cream contains a combination of an antifungal agent and a corticosteroid. It is indicated for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis in patients who are 17 years and older. For tinea pedis infection, clotrimazole/betamethasone should be

used for 2 weeks (no longer than 4 weeks) and for tinea cruris and tinea corporis clotrimazole/betamethasone should only be used for 1 week (no longer than 2 weeks). Clotrimazole/betamethasone cream demonstrated better results in clinical studies than either of the agent used individually. The generic combination product of clotrimazole/betamethasone dipropionate cream may also be more cost-effective than the individual components.

Recommendation

It is recommended to add clotrimazole/betamethasone combination product to the current formulary as it may provide some cost-effectiveness over the individual products. In addition, the ease of use of the combination product may be beneficial.

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Appendix C

Risperidone Extended Release Injection (Perseris®)

Classification: Atypical antipsychotic drug

Pharmacology:

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:

Pharmokinetic Parameter	Details
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.

Pharmokinetic Parameter	Details
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:

Perseris® is indicated for the treatment of schizophrenia in adults.

Dosage:

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. Perseris® does not require oral overlap or loading dose

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 I 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 90mg, 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.

Perseris® has not been studied in patients with renal or hepatic impairment and should be used with caution these groups of patients

Contraindications:

Hypersensitivity to risperidone, its metabolite, 9-hydroxyrisperidone, or the Atrigel system or its components (poly DL-lactide-co-glycolide polymer and *N*-methyl-2-pyrrolidone)

Precautions:

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

Interactions:

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:

Adverse reactions from Perseris® have been reported from one double-blind, placebo-controlled study containing 814 adult subjects. The adverse reactions occurring in $\underline{\geq}$ 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. Injection site reaction was similar in both Perseris and placebo groups with most common being injection site pain and erythema (≥ 5%). 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)
Risperidone (Perseris®)	No	90
Risperidone (Perseris®)	No	120

Name	Generic?	Strength (mg)
Risperidone (Risperdal®)	Yes	0.25, 0.5, 1, 2, 3, 4
Risperidone (Risperdal Consta®)	No	12.5, 25, 37.5, 50
Risperidone (Risperdal M-Tab®)	Yes	0.25, 0.5, 1, 2, 3, 4
Paliperidone palmitate (Invega Sustenna®)	No	39, 78, 117, 156, 234

Product Identification and administration:

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. This formulation used ATRIGEL administration system. After injection, the delivery system solidifies upon contact with bodily fluids and the resulting biodegradable implant delivers the drug for a longer period of time depending on dose strength and injection volume.

Efficacy:

Efficacy of Perseris® was demonstrated an 8-week, randomized, double-blind, placebo-controlled study, NCT #02109562 which 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.

Another study that enrolled patients from the 8-week trial previously mentioned, was 52 weeks in duration, multicenter phase 3 open label, outpatient study (NCT02203838) evaluated the long term safety and tolerability of RBP-7000 (Perseris). A secondary outcome of the study assessed long term maintenance of effectiveness. This open label study showed injection site reaction and weigh gain as the most common adverse events. Over the course of the study no significant changes in laboratory measures or EKG was noted as well as vital signs and EPS developments. The mean PANSS score continued to improve over the 12-month period in the rollover participants and remained stable in de novo participants. Data from this open label study was also used to evaluate the long-term impact of Perseris on health-related quality of life, subjective wellbeing, treatment satisfaction nd medication preference in patients with schizophrenia. The analysis concluded that study participants attained health related quality of life scores near that of general US population with over two-thirds reported high satisfaction and preference for Perseris. Satisfaction was noted to increase between week 4 and end of study.

Safety:

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 8 week 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 margins of risperidone were 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:

Perseris® has been shown to be safe and effective in clinical trials with sustained efficacy studied for up to 1 year of treatment. Both 90mg and 120mg doses were shown superior to placebo in their efficacy. There have been no studies showing superiority of Perseris® to oral risperidone or other long acting injectable antipsychotics. Side effect profile for the injection is similar to oral risperidone.

Recommendation:

Overall, current data suggests efficacy of this new formulation of risperidone but 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 patients treated in state hospital settings. Perseris needs to be refrigerated and needs to be reconstituted and a large bore needle (18 G 5/8 inch length needed) is required. 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 (above 4mg/d) and increased cost of use.

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Appendix D

Apixaban (Eliquis®)

Classification:

AHFS Therapeutic Class: 20.12.04 Anticoagulant
Apixaban (Eliquis®) is a direct oral anticoagulant (DOAC) medication used in the treatment and prevention of thrombotic events**.**

Pharmacology:

Apixaban is a reversible selective competitive inhibitor of Factor Xa. Apixaban's mechanism involves inhibition of prothrombinase activity. The result is a decrease in thrombin activation and decrease in thrombus formation.

Indication -FDA & literature supported non-FDA

FDA Labeled Indications (FDA Approval Dec. 28th, 2012):

Arthroplasty of the knee: post-operative deep vein thrombosis (DVT) prophylaxis (px)
Atrial fibrillation (nonvalvular) – cerebrovascular accident; embolism px
DVT treatment
DVT: recurrence px
Total hip replacement: post-operative DVT px
Pulmonary embolism (PE) treatment
PE, recurrence px

Off-label Indications:

Heparin-induced thrombocytopenia (HIT)

Pharmacokinetics

Pharmacokinetic Parameter	Details
Elimination Half-life	15.2 hours (5mg) 6.8 h (2.5mg) Low Body wt: 15.8 h Obesity: 8.8 h
Bioavailability (Oral)	50% (whole, crushed-oral, crushed-nasogastric)
Metabolism	Primarily CYP3A4 Substrate of CYP3A4 and P-glycoprotein
Tmax	3-4 h (10mg) 3.3 h (5mg) 1.5 h (2.5mg)

Pharmacokinetic Parameter	Details
Food Effects	High fat meal: Whole tablet: Tmax increase by 1 hour Crushed Tablets: Cmax decrease 20%, AUC decrease 16%
Protein Binding (Albumin)	Most patients: 87% Hemodialysis: 92-94%
Volume of distribution (Vd)	Most Patients: 21-61 L Low body wt: 52.7 L Obesity: 75.6 L
Excretion	Majority: fecal biliary (mostly unchanged) Renal: 27% (mostly unchanged) Dialysis: 4% removed in 4h Total body clearance: 82.3 mL/min low body weight 68.8mL/min obesity 106.8 mL/min

Dosage/Administration

- Nonvalvular Atrial Fibrillation Embolism px: most patients→ 5 mg orally twice daily (see Dosage Adjustments)
- Post-operative (knee or hip) DVT px: 2.5 mg twice daily beginning 12-24 hours after surgery; hip surgery treatment duration is 35 days. Knee surgery treatment duration is 12 days.
- PE/DVT treatment: 10 mg taken orally twice daily for the first 7 days. Following 7 days, reduce dose to 5 mg orally twice daily.
- DVT/PE: recurrence px: The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE
- Missed dose: If a dose of ELIQUIS is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.
- Temporary interruption for surgery/other intervention: ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

Dosage Adjustments

Geriatric:

- Nonvalvular Atrial Fibrillaation Embolism px meeting at least 2/3 of the following criteria: Age ≥ 80 years, body weight ≤ 60 kg, and/or serum creatinine ≥ 1.5 mg/dL→ use alternate dose: 2.5 mg orally twice daily

Renal:

- Nonvalvular Atrial Fibrillaation Embolism px meeting at least 2/3 of the following criteria: Age ≥ 80 years, body weight ≤ 60 kg, and/or serum creatinine ≥ 1.5 mg/dL→ use alternate dose: 2.5 mg orally twice daily
- DVT/PE px or treatment: No Adjustment

Dialysis:

- DVT/PE px or treatment: No Adjustment
- Stroke prevention: 2.5 mg orally twice daily

Hepatic:

- Mild (Child-Pugh class A): No Adjustment
- Severe (Child-Pugh class C): Not Recommended

Combined P-glycoprotein and strong CYP3A4 inhibitor:

- Decrease dose by 50% in patients receiving more than 2.5 mg twice daily
- Patients already on 2.5 mg twice daily: AVOID

Use in Special Population

Pregnancy - fetal risk cannot be ruled out. Use during labor/delivery in patients receiving neuraxial anesthesia increases risk of epidural hematoma.

Lactation - Not recommended; there is no current data on the presence of apixaban or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Apixaban and metabolites were present in the milk of treated rats.

Geriatrics – avoid in elderly patients with renal clearance below 25 mL/min

Pediatrics - Safety and efficacy not established in pediatric patients

Renal Dysfunction - may require dose adjustment in atrial fibrillation

Hepatic Dysfunction – no adjustment in mild impairment. Avoid in severe impairment (Child-Pugh class C)

Contraindication

Patients with active pathological bleeding

Patients with severe hypersensitivity/anaphylaxis reactions to apixaban

Boxed Warning

Premature discontinuation of apixaban or any oral anticoagulant increases the risk of thrombotic events. Consider an alternative anticoagulant if apixaban treatment is discontinued for any reason other than pathological bleeding or treatment completion.

In patients undergoing neuraxial anesthesia or spinal procedure, epidural or spinal hematoma risk is increased and could result in long term or permanent paralysis. The optimal timing between dosing apixaban and neuraxial procedures is unknown. Monitor patients for signs and symptoms of neurologic impairment and treat urgently. Consider the benefits and risk of neuraxial intervention in patients who are or need to be anticoagulated.

Precautions

- Beer's Criteria: avoid use in elderly with CrCl < 25 mL/min due to increased bleeding risk
- If traumatic epidural or spinal puncture occurs, delay administration for 48 hours
- Prosthetic heart valves: the use of DOAC medication is not recommended
- Concomitant use with P-glycoprotein and strong CYP3A4 inducers (Ex: rifampin, carbamazepine, phenytoin, St. John's wort)
- Concomitant use with P-glycoprotein and strong CYP3A4 inhibitors (Ex: ketoconazole, itraconazole, ritonavir)
- Elective procedures: procedures bearing a risk of bleeding may require interruption in therapy beginning 48 hours prior when the risk of bleeding is moderate to high, or 24 hours prior if the bleeding risk is low.
- Exercise caution in patients with postoperative indwelling catheters. Do not remove earlier than 24 hours following the last apixaban dose.
- Serious and potentially fatal bleeding can occur, particularly with concomitant use of other medications that affect hemostasis (Ex: aspirin, antiplatelets, NSAIDs, SSRI, SNRI, thrombolytics, other anticoagulants)
- Anticoagulation may persist for 24 hours beyond the last apixaban dose. Activated charcoal reduces absorption. An anti-factor Xa reversal agent is available.
- Severe hepatic impairment: Use is not recommended
- ESRD requiring dialysis, advanced age (≥80 years old), low body weight (≤ 60 kg): dose adjustment may be necessary
- PE in the setting of hemodynamic instability, as well as patients who may require thrombolysis or pulmonary embolectomy: use not recommended

Sentinel Event Advisory: SEA #61 (Effective July 1st, 2019)

- Create name awareness of the various DOACs among providers, including pharmacists, emergency department (ED) clinicians, and others who may be called on to deal with life-threatening bleeding problems.
- Use evidence-based protocols and practice guidelines for drug initiation and maintenance, anticoagulation reversal, management of bleeding events, and perioperative management for each DOAC.
- Have a written policy in place requiring baseline and ongoing lab tests to monitor and adjust anticoagulant therapy.
- Each particular DOAC's indications for use should be included on the patient's prescription, in instructions for the patient, and in the electronic medical record.
- Address anticoagulation safety practices by evaluating them and setting goals to improve measures, and establishing a process to identify, respond to, and report adverse drug events.
- Provide education to patients and families about the anticoagulant medication prescribed, including adherence to medication dose and schedule, follow-up appointments, potential drug-drug interactions (and interactions with herbs or supplements), the potential for adverse drug reactions and how to spot them, and when to contact a physician or visit the ED.

Adverse Effects

- **Common Adverse Effects (≥ 10%)**: Hemorrhage (overall ≤ 15%; major ≤ 2%, clinically relevant non-major bleeding 4%)
- **Common Adverse Effects (≥ 1%)**: contusion, bleeding gums, hematoma, hematuria, rectal hemorrhage, nausea, menorrhagia, epistaxis, hemoptysis
- **Undefined frequency**: Cardiovascular: Thrombosis (with premature discontinuation)
- **Central nervous system:** Epidural intracranial hemorrhage (in patients receiving neuraxial anesthesia or undergoing spinal puncture)
- **Hematologic & oncologic**: Spinal hematoma (in patients receiving neuraxial anesthesia or undergoing spinal puncture)

Monitoring

- Monitoring – Anticoagulation monitoring is not required. However, it provides utility in trauma, urgent procedures/interventions, major bleeding, overdose/suicide attempt, potential interaction, acute thrombosis, liver/renal failure, or adherence verification.
- High risk patients: HAS-BLED risk score (**H**ypertension, **A**bnormal renal and liver function, **S**troke, **B**leeding, **L**abile INRs, **E**lderly, and **D**rugs/alcohol.

Drug-Drug Interactions

Defibrotide (CONTRAINDICATED): increased bleed risk
P-glycoprotein and Strong CYP3A4 inducers (MAJOR): decreased apixaban levels, thrombotic risk *(Examples: rifampin, carbamazepine, phenytoin, St. John's wort)*
Strong CYP3A4 inhibitors (MAJOR): increased apixaban levels, bleeding risk *(Examples: ketoconazole, itraconazole, ritonavir)*
Fibrinolytics (MAJOR): increased bleed risk
Anticoagulant/antiplatelet agents (MAJOR): increased bleed risk

Efficacy

ADVANCE Trials:

Double blind non-inferiority efficacy comparison of apixaban versus enoxaparin in the prophylaxis of deep vein thrombosis following hip or knee replacement surgery. 11,659 patients were randomized in three trials. In all 3 trials, the primary endpoint was a composite of adjudicated asymptomatic and symptomatic DVT, nonfatal PE, and all-cause death at the end of the double-blind intended treatment period.

ADVANCE 1 determined apixaban to be non-inferior to enoxaparin in the primary endpoint. ADVANCE 2 & 3 found apixaban to be superior at meeting the primary endpoints. In all three trials, there were no significant differences in clinically significant bleeding.

Figure 1. ADVANCE 1 & 2 Trial Results

Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery*

	ADVANCE-1			ADVANCE-2		
Events during 12-day treatment period	ELIQUIS 2.5 mg po bid	Enoxaparin 30 mg sc q12h	Relative Risk (95% CI) P-value	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1157**	**N=1130**		**N=976**	**N=997**	
Total VTE†/All-cause death	104 (8.99%) (7.47, 10.79)	100 (8.85%) (7.33, 10.66)	1.02 (0.78, 1.32) NS	147 (15.06%) (12.95, 17.46)	243 (24.37%) (21.81, 27.14)	0.62 (0.51, 0.74) p<0.0001
Number of Patients	**N=1599**	**N=1596**		**N=1528**	**N=1529**	
All-cause death	3 (0.19%) (0.04, 0.59)	3 (0.19%) (0.04, 0.59)		2 (0.13%) (0.01, 0.52)	0 (0%) (0.00, 0.31)	
PE	16 (1.0%) (0.61, 1.64)	7 (0.44%) (0.20, 0.93)		4 (0.26%) (0.08, 0.70)	0 (0%) (0.00, 0.31)	
Symptomatic DVT	3 (0.19%) (0.04, 0.59)	7 (0.44%) (0.20, 0.93)		3 (0.20%) (0.04, 0.61)	7 (0.46%) (0.20, 0.97)	
Number of Patients	**N=1254**	**N=1207**		**N=1192**	**N=1199**	
Proximal DVT‡	9 (0.72%) (0.36, 1.39)	11 (0.91%) (0.49, 1.65)		9 (0.76%) (0.38, 1.46)	26 (2.17%) (1.47, 3.18)	
Number of Patients	**N=1146**	**N=1133**		**N=978**	**N=1000**	
Distal DVT‡	83 (7.24%) (5.88, 8.91)	91 (8.03%) (6.58, 9.78)		142 (14.52%) (12.45, 16.88)	239 (23.9%) (21.36, 26.65)	

* Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

† Total VTE includes symptomatic and asymptomatic DVT and PE.

‡ Includes symptomatic and asymptomatic DVT.

Figure 2. ADVANCE 3 Trial Results

Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Hip Replacement Surgery*

	ADVANCE-3		
Events During 35-Day Treatment Period	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1949**	**N=1917**	
Total VTE†/All-cause death	27 (1.39%) (0.95, 2.02)	74 (3.86%) (3.08, 4.83)	0.36 (0.22, 0.54) p<0.0001
Number of Patients	**N=2708**	**N=2699**	
All-cause death	3 (0.11%) (0.02, 0.35)	1 (0.04%) (0.00, 0.24)	
PE	3 (0.11%) (0.02, 0.35)	5 (0.19%) (0.07, 0.45)	
Symptomatic DVT	1 (0.04%) (0.00, 0.24)	5 (0.19%) (0.07, 0.45)	
Number of Patients	**N=2196**	**N=2190**	
Proximal DVT‡	7 (0.32%) (0.14, 0.68)	20 (0.91%) (0.59, 1.42)	
Number of Patients	**N=1951**	**N=1908**	
Distal DVT‡	20 (1.03%) (0.66, 1.59)	57 (2.99%) (2.31, 3.86)	

*Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

†Total VTE includes symptomatic and asymptomatic DVT and PE.

‡Includes symptomatic and asymptomatic DVT.

AMPLIFY and AMPLIFY-EXT Trials:

AMPLIFY and AMPLIFY-EXT trials examined the safety and efficacy of apixaban for the treatment of DVT and PE, and for risk reduction of recurrent DVT and PE following 6 to 12 months of treatment. Both studies were randomized, parallel-group, double-blind trials in patients with symptomatic proximal DVT and/or symptomatic PE. In AMPLIFY, the primary objective of non-inferiority to enoxaparin/warfarin for the incidence of recurrent VTE was met. Randomization

included 5244 and 2482 patients respectively. Apixaban was determined to be non-inferior to warfarin/enoxaparin.

AMPLIFY-EXT compared two doses of apixaban against placebo, 2.5 mg twice daily and 5 mg twice daily. The primary endpoint was met, concluding that both doses were superior to placebo.

Figure 3. AMPLIFY Trial Results

Efficacy Results in the AMPLIFY Study

	ELIQUIS N=2609 n	Enoxaparin/Warfarin N=2635 n	Relative Risk (95% CI)
VTE or VTE-related death*	59 (2.3%)	71 (2.7%)	0.84 (0.60, 1.18)
DVT†	22 (0.8%)	35 (1.3%)	
PE†	27 (1.0%)	25 (0.9%)	
VTE-related death†	12 (0.4%)	16 (0.6%)	
VTE or all-cause death	84 (3.2%)	104 (4.0%)	0.82 (0.61, 1.08)
VTE or CV-related death	61 (2.3%)	77 (2.9%)	0.80 (0.57, 1.11)

* Noninferior compared to enoxaparin/warfarin (P-value <0.0001).

† Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Figure 4. AMPLIFY-EXT Trial Results

Efficacy Results in the AMPLIFY-EXT Study

				Relative Risk (95% CI)	
	ELIQUIS 2.5 mg bid N=840	ELIQUIS 5 mg bid N=813	Placebo N=829	ELIQUIS 2.5 mg bid vs Placebo	ELIQUIS 5 mg bid vs Placebo
	n (%)				
Recurrent VTE or all-cause death	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22, 0.48) p<0.0001	0.36 (0.25, 0.53) p<0.0001
DVT*	19 (2.3)	28 (3.4)	72 (8.7)		
PE*	23 (2.7)	25 (3.1)	37 (4.5)		
All-cause death	22 (2.6)	25 (3.1)	33 (4.0)		

*Patients with more than one event are counted in multiple rows.

ARISTOTLE Trial:

ARISTOTLE trial compared the efficacy of apixaban versus warfarin in preventing thromboembolic event in patients with non-valvular atrial fibrillation. Participants met one or more of the following criteria: prior stroke/TIA, prior embolism, ≥75 years of age, medically managed hypertension, heart failure (≥NYHA Class 2), left ventricular ejection fraction ≤ 40%. A total of 18,201 patients were randomized and followed for an average of 89 weeks.

Apixaban proved superior to warfarin at reducing risk of stroke or embolism. Apixaban was also associated with fewer major bleeds when compared with warfarin.

Figure 5. ARISTOTLE Trial Results

Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE (Intent-to-Treat Analysis)

	ELIQUIS N=9120 n (%/year)	Warfarin N=9081 n (%/year)	Hazard Ratio (95% CI)	P-value
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.01
Stroke	199 (1.19)	250 (1.51)	0.79 (0.65, 0.95)	
Ischemic without hemorrhage	140 (0.83)	136 (0.82)	1.02 (0.81, 1.29)	
Ischemic with hemorrhagic conversion	12 (0.07)	20 (0.12)	0.60 (0.29, 1.23)	
Hemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Unknown	14 (0.08)	21 (0.13)	0.65 (0.33, 1.29)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	

The primary endpoint was based on the time to first event (one per subject). Component counts are for subjects with any event, not necessarily the first.

Current Formulary Options/Alternatives

Fondaparinux (Arixtra®)
Enoxaparin sodium (Lovenox®)
Heparin sodium
Rivaroxaban (Xarelto®)
Warfarin sodium (Jantoven®,Coumadin®)

Dosage Forms/Cost

Brand only: Eliquis® 2.5 mg oral tablet, 5 mg oral tablet, & 30 day DVT/PE Starter Pack (5 mg oral tablet)

Pharmacoeconomics: Comparison with alternative, rivaroxaban (Xarelto®): Note pricing data is based on retail claims analyzed by goodrx and wellrx, as well as wholesaler pricing data from November 2019. This pricing data is subject to constant fluctuation and should be reviewed on a case-case basis. Pricing is based on one month supply at maintenance doses and may not reflect induction dosing.

Goodrx (outpatient):

- Apixaban Medicare Part D copay range: $19-521; goodrx coupon: $448
- Rivaroxaban Medicare Part D copay range: $19-523; goodrx coupon: $452

Wellrx (lowest cash price in zip code 78223):

- Apixaban: $446.59 (HEB)
- Rivaroxaban: $450.39 (HEB)

Pharmacy Cost through wholesaler:

- Apixaban: $426 (awp $538)
- Rivaroxaban: $430 (awp $533)

Cost Comparison Conclusion: When treating DVT/PE, both medications require an induction dose that could result in partial bottles. The cost difference between the two comparators is not significant factor for inpatient treatment. However, for patients with insurance coverage, or anticipated discharge, the preferred agent on a patient's insurance formulary may influence the selection after clinical factors have been considered.

Special Considerations

Toxicity

Acute Ingestion of Toxic dose: Activated charcoal can be administered if suspicion of recent potentially toxic dose. Seek immediate medical attention. (can be administered prior to hospital)

Reversal Agent: Recombinant Factor Xa (Andexxa®) (to be administered in hospital)

Special Considerations

Switching from warfarin to apixaban: discontinue warfarin and initiate apixaban when INR is below 2

Switching from apixaban to warfarin: discontinue apixaban and start warfarin at the time of the next apixaban dose would have been due. At the start of warfarin, bridge with a parenteral anticoagulant until the INR is in therapeutic range.

Switching from apixaban to anticoagulant other than warfarin (oral or parenteral). Discontinue apixaban and initiate the alternative at the time the next apixaban dose would have been due.

Switching from anticoagulant (oral or parenteral) other than warfarin to apixaban. Discontinue anticoagulant and initiate apixaban at the time the next dose would have been due.

Surgery (when procedure site protocol is unspecified) Discontinue apixaban 48 hours prior to procedures with a moderate to high risk of clinically significant bleeding. Discontinue 24 hours prior to procedures with a low bleed risk or where bleeding could be easily controlled. Bridging is generally not required.

Resume apixaban following the procedure, when the patient is hemodynamically stable.

Summary/Conclusion

Apixaban is a DOAC medication indicated for the treatment and prevention of thrombotic events. Use of any anticoagulant agent is accompanied by a risk of bleeding. However, apixaban offers a reasonable side effect profile for patients requiring anticoagulation. The advent of not requiring constant lab monitoring may offset the current price difference between alternative agents. The oral dosage form and recent approval of a reversal agent further promote its utility.

Recommendation

Apixaban should be added to the formulary.

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