KY Medicaid Proposed Formulary Changes

Effective 10/1/2017 (unless otherwise noted)

Table 1: Summary of Medicaid PDL proposed designation as **Preferred**

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Adoxa	Doxycycline monohydrate	Tablet	75 mg	**Effective 7/1/17.**	Approved
Multiple	Doxycycline hyclate	Capsule	50 mg, 100 mg	**Effective 7/1/17.**	Approved
Multiple	Doxycycline hyclate	Tablet	20 mg, 100 mg	**Effective 7/1/17.**	Approved
Strattera	Atomoxetine	Capsule	10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg	Generic launch 5/2017. Remove step.	Approved

Table 2: Summary of Medicaid PDL proposed designation as **Non-Preferred**

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	
Lartruvo	Olaratumab	Solution, Intravenous	190 mg/19 mL, 500 mg/50 mL	Block on pharmacy benefit. Require prior authorization on medical benefit.	Approved
Leukine	Sargramostim	Solution – Injection and Intravenous	250 mcg, 500 mcg/mL		Approved
Rubraca	Rucaparib	Tablet	200 mg, 250 mg, 300 mg		Approved
Soliqua	Insulin glargine and lixisenatide	Subcutatneous Solution, Pen-Injector	100 units/33 mcg		Approved
Spinraza	Nusinersen	Intrathecal Solution	12 mg/5mL	Block on pharmacy benefit. Require prior authorization on medical benefit. Criteria approved via e-vote.	Approved

New Drugs

Reviewed for P&T Meeting June 15, 2017

Lartruvo (olaratumab)

Therapeutic Class: PDGFR-alpha blocker (antineoplastic)
FDA indication: Soft Tissue Sarcoma
Formulary Recommendations: Non-preferred, Medical benefit only
Rationale: Surgical resection is the standard primary treatment for localized STS with neoadjuvant or adjuvant radiation therapy and/or chemotherapy also being used. For advanced, unresectable or metastatic disease, single agent chemotherapy or anthracycline-based combination chemotherapy have been used. The NCCN Guidelines for STS have not been updated to include Lartruvo. Approval was based on one small, open-label, randomized trial evaluating the safety and efficacy of Lartruvo which showed the overall survival with Lartruvo was 26.5 months compared to 14.7 months in the doxorubicin-alone group. An ongoing randomized, double-blind, placebo-controlled, phase III trial of Latruvo + doxorubicin versus placebo + doxorubicin in patients with advanced or metastatic STS is currently ongoing but results are not yet available in published literature.
P&T Decision: Approved

Rubraca (rucaparib)

Therapeutic Class: PARP inhibitor (antineoplastic agent)
FDA indication: Advanced ovarian cancer
Formulary Recommendations: Non-preferred
Rationale: Rubraca received accelerated approval based on two multi-center, single-arm, open-label clinical trials. The observational data from the trials indicate that Rubraca may slow or prevent growth of ovarian cancer based on x-rays of tumor size; however, there was no comparison to placebo or other therapies. No evidence has shown Rubraca improves survival, quality of life or symptoms. The NCCN Guidelines for ovarian cancer have been update to include Rubraca as a possible targeted recurrence therapy.
P&T Decision: Approved

Soliqua (insulin glargine and lixisenatide)

Therapeutic Class: Long-acting insulin + GLP-1 receptor agoinst
FDA indication: Type 2 diabetes
Formulary Recommendation: Non-preferred
Rationale: Overall, there is a lack of clear benefit in adding Soliqua as a preferred product at this time. A second drug in this class was recently launched as well with similar advantages and disadvantages. We plan to reevaluate decisions and potential initiatives with this new class of agents later this year.
P&T Decision: Approved

Spinraza (nusinersen)

Therapeutic Class: Antisense oligonucleotide
FDA indication: Spinal muscular atrophy in pediatric and adult patients
Formulary Recommendation: Non-preferred**,** Medical benefit only, Previously approved via e-vote 5/17/17
Rationale: The application for drug approval for nusinersen was grated fast track designation and priority review. However, the ENDEAR trial, which was the main basis for the rushed approval has not yet had full results published. Additional open-label students were uncontrolled lacking a control group but findings appeared generally supportive and similar to efficacy results seen in the ENDEAR trial. There are additional studies which are active and/or still recruiting patients.
P&T Decision: Approved

Pharmacy &Therapeutics Committee Summary Review
Lartruvo - olaratumab (Eli Lilly)

Prepared by: Michael Kapraly, PharmD Candidate 2018 **Presentation Date:** July 6, 2017

Therapeutic Class: PDGFR-alpha blocker **FDA Approval Date:** 10/19/16

FDA Indication: Soft Tissue Sarcoma (STS)

Comparable Formulary Products: Dacarbazine, Ifosfamide + mesna

Proposed Designation & Rationale

Recommendation: Non-Preferred, Medical benefit ONLY

- Criteria for use:
  - Diagnosis = Soft tissue sarcoma with histologic subtype (locally advanced or metastatic) for which an anthracycline-containing regimen is appropriate and not previously treated with an anthracycline
  - Age 18 years or older
  - Prescribed by an oncologist
  - Documentation that curative radiotherapy or surgery is not an option
  - Must be used in combination with doxorubicin for the first 8 cycles (each 3 weeks)
  - Reauthorization criteria: Initial criteria plus no disease progression or unacceptable toxicity
  - Dosage allowed = two 15 mg/kg infusions every 21 days
- Initial approval duration = 24 weeks, Reauthorization approval duration = 12 months

Clinical Implications/Place in Therapy:
Surgical resection is the standard primary treatment for localized STS with neoadjuvant or adjuvant radiation therapy and/or chemotherapy also being used. For advanced, unresectable or metastatic disease, single agent chemotherapy or anthracycline-based combination chemotherapy have been used. The NCCN Guidelines for STS have not been updated to include Lartruvo. One small, randomized trial evaluating the safety and efficacy of Lartruvo was used to grant accelerated approval. The trial was open-label; however, the overall survival data presented for Lartruvo was 26.5 months compared to 14.7 months in the doxorubicin-alone group. An ongoing randomized, double-blind, placebo-controlled, phase III trial of Latruvo + doxorubicin versus placebo + doxorubicin in patients with advanced or metastatic STS is currently ongoing but results are not yet available in published literature.

Clinical Pharmacology: Lartruvo is a recombinant IgG1 MAB that binds to PDGFR-alpha, blocking PDGF-AA, BB, and CC binding and receptor activation. The PDGF pathway plays a significant role in tumor cell cell signaling, differentiation, growth, and angiogenesis. Based on the preclinical data, Lartruvo by itself or in combination with doxorubicin is shown to have effect in soft tissue sarcoma.[1]

Notable Pharmacokinetics: $T_{1/2}$ at the doses recommended by the package insert (15 mg/kg) was a range of 6.04-9.38 days after the first dose, and 8.25 days after multiple doses.[5]

Efficacy:

Trial Design/ Population	Groups	Outcomes	Results
Two part open label trial with 15 patients in the phase 1b portion and 129 patients in the phase 2 portion[1]	15 patients studying safety endpoints, 64 patients in Lartruvo + doxorubicin arm, and 65 patients in the doxorubicin monotherapy arm	Primary outcome: Progression free survival Secondary: overall survival, objective response rate, safety, and PK data	Significantly better progression free survival, overall survival, and objective response rate in the Lartruvo + doxorubicin arm

16 patients over 20 yo with advanced primary or recurrent solid tumors not responding to standard therapy or who had no standard therapy available were placed in a single center open label dose escalation phase 1 trial[5]	One group - 16 patients	Evaluate presence and frequency of ADRs and monitor PK data	Side effects were generally mild-to-moderate in severity. They will be discussed later in the paper

Conclusion: At the moment, there is only one study published that studies the comparative efficacy of Lartruvo and doxorubicin to doxorubicin alone. No other studies exist that compare other combination therapies for soft tissue sarcoma. Until there is more data comparing the efficacy of Lartruvo and doxorubicin against these other therapy options, I would not recommend this drug be added to formulary.

Ongoing Clinical Trials:

- Doxorubicin With Upfront Dexrazoxane Plus Olaratumab for the Treatment of Advanced or Metastatic Soft Tissue Sarcoma
- A Study of Olaratumab (LY3012207) in Participants With Soft Tissue Sarcoma, A Study of Olaratumab (LY3012207) in Participants With Advanced Soft Tissue Sarcoma (ANNOUNCE)[6]

Contraindications: None listed at this time

Warnings/Precautions: Lartruvo is known to cause hematologic abnormalities, infusion site reactions, as well as moderate-to-severe nausea and vomiting[3,5,7]

Drug Interactions: Should not be administered concomitantly with intravesical BCG, deferiprone, clozapine, or dipyrone. It may increase the levels of clozapine and deferiprone. Dipyrone may increase the levels of Lartruvo. Lartruvo may decrease the effects of intravesical BCG[2]

Common Adverse Effects:

- > 20%: proteinuria, nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, cough, constipation, chills, hypersensitivity reactions, infusion reaction, decreased appetite, tumor hemorrhage, abdominal pain, neuropathy, headache
- Lab abnormalities > 20%: lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated aPTT, hypokalemia, increased alkaline phosphatase, increased AST, and hyperphosphatemia[3,5,7]

Safety:

- *Sound Alike Look Alike* - ***None at this time***[8]
- *REMs Program Requirement* - ***None at this time***[9]
- *Known safety issues (ISMP safety alerts)* ***None at this time***

Dosage/Administration: 15 mg/kg IV over 60 minutes on days 1 and 8 of a 3 week cycle until disease progression or therapy-limiting toxicity. Doxorubicin is administered concomitantly at 75 mg/m^2 IV on day 1 of each 3 week cycle for a total of 8 cycles. One study allowed dexrazoxane to be substituted for doxorubicin during cycles 5-8 to reduce the potential for cardiotoxicity that is prevalent in doxorubicin therapy. Dosage was not specified.[1,3,5]

Special Drug Monitoring: Lymphopenia, Neutropenia, Thrombocytopenia, Hyperglycemia, aPTT, Potassium, Alkaline phosphatase, AST, Phosphate[1,3,7]

Handling and Preparation: Product should not be shaken or frozen. Once product has been diluted, it may be stored up to 24 hours in

refrigerated temperature (2-8^{O}C) and up to 4 hours after in room temperature (<25^{O}C). Storage time includes the duration of infusion. Vials that are not fully used should be discarded.[3,10]

Financial Impact:

- Over 12,000 new cases of soft tissue sarcoma are diagnosed every year. They are a rare but serious group of malignant tumors that comprise < 1% of adult malignancies, but comprise almost 12% of pediatric malignancies.[11]
- *Estimated acquisition cost and annual budget impact:* $2360 WAC. $78.67 per vial, with 2-3 vials being used for a typical patient. With doxorubicin, the total cost is most likely $494-652 per cycle during the cycles that doxorubicin is used.It should be noted that cost is calculated **per cycle**, which in this case is a 3 week cycle.[2,10]
- *Manage-care costs:* Cost of drug, cost of antiemetic therapy, cost of monitoring for lab abnormalities, cost of diphenhydramine for prophylaxis of infusion reactions[3]
- *Pharmacoeconomic data:* No pharmacoeconomic data exists for this drug at this time

References:

1. Tap W, Jones R, Van Tine B, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 2016;388:488-97. http://dx.doi.org/10.1016/S0140-6736(16)30587-6.
2. Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; March 7,2017.
3. Lartruvo package insert - http://medlibrary.org/lib/rx/meds/lartruvo/
4. National Comprehensive Cancer Network. Soft Tissue Sarcoma (Version 2.2017).
5. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed 3/19/2017.
6. Doi T, Ma Y, Dontabhaktuni A, et al. Phase 1 Study of olaratumab in Japanese patients with advanced solid tumors. Cancer Sci 2014;105: 862-869. doi: 10.1111/cas.12444
7. US National Institutes of Health. Lartruvo. https://clinicaltrials.gov/ct2/results?term=lartruvo&Search=Search. Accessed 3/19/2017.
8. Chiorean E, Youssoufian H, and Loizos N et al. A Phase 1 study of olaratumab, an anti-platelet-derived growth factor receptor alpha (PDGFRα) monoclonal antibody, in patients with advanced solid tumors. Cancer Chemother Pharmacol 2014;73:595-604.
9. Institute for Safe Medication Practices. ISMP's List of Confused Drug Names.
10. http://www.ismp.org/Tools/confuseddrugnames.pdf. Accessed 3/19/2017.
11. American Society of Health System Pharmacy. REMS Database.
12. https://www.ashp.org/Pharmacy-Practice/Pharmacy-Topics/REMS/REMS-Database. Accessed 3/19/2017.
13. Lartruvo Product Distribution and Specifications. Eli Lilly website.
14. https://www.lartruvo.com/_assets/pdfs/Olara-Distribution-Resource-Electronic.pdf Accessed March 19, 2017.
15. Siegel R, Miller K, Jemal A. Cancer Statistics, 2017. A Cancer Journal for Clinicians 2017;67(1):7-30.

Pharmacy &Therapeutics Committee Summary Review
Rubraca® (rucaparib) – Clovis Oncology

Prepared by: CVS Health / Jessica Hatton **Presentation Date:** July 6, 2017

Therapeutic Class[1]: PARP Inhibitor, Antineoplastic Agent **FDA Approval Date[1]:** December 19, 2016

FDA Indication[1]: Advanced ovarian cancer as monotherapy for deleterious germline and/or somatic BRCA mutation associated (as detected by an approved test) advanced ovarian cancer in patients who have been treated with 2 or more prior lines of chemotherapy.

Comparable Formulary Products: No PARP inhibitors are preferred. Other agents: Lynparza (approved 2014), Zejula (approved March 2017)

Proposed Designation and Rationale[2,3]

Recommendation: Non-Preferred

- Criteria for use:
  - Diagnosis = Advanced or metastatic ovarian cancer
  - Member is female and age 18 years or older
  - Prescribed by an oncologist
  - Documentation of deleterious BRCA mutation submitted
  - At least two prior chemotherapy regimens have been ineffective or not tolerated
  - No prior use of PARP inhibitors
  - Rubraca will be used as monotherapy
  - Reauthorization criteria: Initial criteria plus no disease progression or unacceptable toxicity
  - Dosage allowed = up to 600 mg per day, 30 day supply
- Initial approval duration = 6 months, Reauthorization approval duration = 12 months

Clinical Implications/Place in Therapy:
Rubraca is FDA approved under accelerated approval based on two multi-center, single-arm, open-label clinical trials. The observational data from the trials indicate that Rubraca may slow or prevent growth of ovarian cancer based on x-rays of tumor size; however, there was no comparison to placebo or other therapies. No evidence has shown Rubraca improves survival, quality of life or symptoms. The NCCN Guidelines for ovarian cancer have been update to include Rubraca as a targeted recurrence therapy.

Ongoing Clinical Trials:

- Absorption, Metabolism, and Excretion Following a Single Oral Dose of [14C]-Rucaparib
- ARIEL4: A Study of Rucaparib Versus Chemotherapy BRCA Mutant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Patients
- A Study of Rucaparib in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency
- A Study of Oral Rucaparib in Patients With a Solid Tumor (Phase I) or With gBRCA Mutation Ovarian Cancer (Phase II)
- A Combination Study of Rucaparib and Atezolizumab in Participants With Solid Tumors and Advanced Gynecologic Cancers, With a Focus on
- A Study of Rucaparib in Patients With Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (ARIEL2)
- A Study to Assess the Efficacy of Rucaparib in Metastatic Breast Cancer Patients With a BRCAness Genomic Signature
- A Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients With Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer
- A Study of Rucaparib Verses Physician's Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency
- Pharmacokinetic Drug-Drug Interaction Study of Rucaparib
- Rucaparib in BRCA1/2 or PALB2 Mutated Pancreatic Cancer
- PARP Inhibition for Triple Negative Breast Cancer (ER-/PR-/HER2-)With BRCA1/2 Mutations

References:

1. Rubraca (rucaparib) tablets, for oral use [prescribing information]. Boulder, CO: Clovis Onclolgy, Inc. February 2017.
2. National Comprehensive Cancer Network. Ovarian Cancer (Version 1.2017).
3. US National Institutes of Health. Rubraca. https://clinicaltrials.gov/ct2/results?term=rucaparib&Search=Search
4. CVS Health. CVS Caremark Pharmacy & Therapeutics Drug Monograph: Rubraca (rucaparib) tablets. February 22, 2017.

Pharmacy &Therapeutics Committee Summary Review
Soliqua® (insulin glargine and lixisenatide) – Sanofi-Aventis

Prepared by: Vineeta Rao, PharmD Candidate 2019 **Presentation Date:** July 6, 2017

Therapeutic Class: Long-acting insulin and GLP-1 receptor agonist **FDA Approval Date:** November 21, 2016

FDA Indication:[1] Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide

Comparable Formulary Products: There are no comparable products as this is a new combination of medications to treat diabetes. However, each ingredient in the product is available individually. Insulin glargine is available as Basaglar. Incretin mimetics available include Victoza (liraglutide) and Trulicity (dulaglutide).

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:
  - Diagnosis = Type 2 diabetes
  - Clinical reason supported by chart notes why the trial agents listed below cannot be used
    - 30 day trial of Insulin Glargine (Lantus or Basaglar) AND a GLP-1 agonist (Victoza, Trulicity, Bydureon, Byetta, or Tanzeum) separately taken together at the same time
- Approval duration = 12 months

Clinical Implications/Place in Therapy:

Soliqua belongs to a new class of agents that combine a basal insulin with a GLP-1 agonist. Soliqua would be prescribed for a Type 2 diabetic patient who has tried and failed to achieve adequate A1C reduction with the following therapies: 1) first-line oral therapies for Type 2 diabetes such as Metformin, 2) GLP-1 agonists, and 3) basal insulin regimens. Advantages to Soliqua include potentially lower cost and comparable ease of administration to other GLP-1 agonists. Studies show that Soliqua achieves greater reductions in A1C compared to both insulin glargine alone and lixisenatide alone. Soliqua has a low side effect profile and shows no greater incidence of hypoglycemic episodes compared to insulin. Soliqua also has the added benefit of controlling A1C without causing weight gain; in some cases, patients experienced weight loss while taking Soliqua. Disadvantages include the fixed ratio aspect of Soliqua, making it difficult to titrate the two medications to achieve optimal glycemic control. Additionally, patients who have failed other therapies may be insulin-resistant; the maximum dose of 60 units of insulin in Soliqua may not be sufficient for glycemic control. The advantage of Soliqua over a GLP-1 agonist alone in patients who are insulin-naïve but have failed oral therapy has not yet been clearly demonstrated, although ongoing clinical trials are currently investigating this comparison. A second drug in this class was recently launched as well with similar advantages and disadvantages. Overall, there is a lack of clear benefit in adding Soliqua as a preferred product and we will reevaluate decisions and potential initiatives with this new class of agents later this year.

Clinical Pharmacology:[1]

Insulin glargine: regulates glucose metabolism. Insulin glargine lowers blood glucose by
1) stimulating peripheral glucose uptake, especially by skeletal muscles and fat
2) inhibiting hepatic glucose production
3) inhibits lipolysis and proteolysis and enhances protein synthesis.

The long-acting formulation of insulin glargine allows it to mimic human basal insulin.

Lixisenatide is a GLP-1 receptor agonist that
1) increases glucose-dependent insulin release
2) decreases glucagon secretion
3) slows gastric emptying

Notable Pharmacokinetics: [1]

- Compared to lixisenatide alone, the Cmax of Soliqua is lower whereas AUC is generally comparable.
- The ratio of insulin glargine/lixisenatide has no clinically relevant impact on the pharmacokinetics of either insulin glargine or lixisenatide

Efficacy:[2,3]

Table 1: Insulin glargine/lixisenatide vs monocomponents

Trial Design/ Population	Groups	Outcomes	Results
Open-label, randomized, parallel-group, multicenter phase III trial in Type 2 DM patients who showed inadequate glycemic control after at least 3 months of treatment with Metformin or other oral glucose-lowering therapy.	**Intervention**: Received insulin glargine/lixisenatide once daily. Patients were first given medications in a 2:1 ratio of 2 units of glargine to 1 unit of lixisenatide. The dose was started at 10 units insulin/5 mcg lixisenatide and titrated up to 40 units/20 mcg. Once this dose was reached, patients were switched to a 3:1 ratio of insulin/lixisenatide. **Control groups:** 1) Insulin therapy only: once daily Lantus Solostar with a max dose of 60 units per day 2) Lixisenatide therapy only: initial dose of 10 mcg once daily for the first two weeks, then 20 mcg for the maintenance dose	**Primary endpoint:** • HbA1c reduction **Secondary endpoint:** • Percentages of patients reaching HbA1c < 7% and less than 6.5% • Composite endpoints of HbA1c < 7% with no weight gain • HBbA1c < 7% with no documented symptomatic hypoglycemia • HbA1c < 7% with no weight gain and no documented symptomatic hypoglycemia **Safety endpoints:** • Symptomatic hypoglycemia • Adverse effects such as allergic reactions, major cardiovascular events, and pancreatic events	**Primary endpoint:** • Mean for Soliqua group: 6.5% • Mean for insulin group: 6.8% • Mean HbA1c for lixisenatide group: 7.3% **Secondary endpoint:** • A significantly higher percentage of patients receiving Soliqua reached HbA1c < 7% or < 6.5% • Body weight increased for insulin group but decreased for both the Soliqua and the lixisenatide group • A higher proportion of patients in the Soliqua group achieved HbA1c < 7% with no documented symptomatic hypoglycemia than either monotherapy group • A higher proportion of patients in the Soliqua group achieved HbA1c < 7% with no weight gain and no documented symptomatic hypoglycemia than either monotherapy group **Safety**: • Hypoglycemia incidence was similar between insulin and Soliqua group. Less incidence of hypoglycemia in the lixisenatide group. • ADRs: overall, Soliqua was well-tolerated. Most common ADRs were nausea and diarrhea, and they subsided over time. Vomiting was less common in Soliqua group than lixisenatide. **Overall conclusion:** Soliqua achieves more meaningful HbA1c reduction than either insulin or lixisenatide alone without causing weight gain. It has no increased risks of hypoglycemia compared to insulin alone.

Table 2: Insulin glargine/lixisenatide vs insulin glargine alone

Trial Design/Population	Groups	Outcomes	Results
Open-label, randomized phase III trial in Type 2 DM patients who showed inadequate glycemic control on basal insulin with or without up to two oral glucose-lowering agents.	**Intervention:** Received insulin glargine/lixisenatide once daily, titrated to fasting plasma glucose <100 mg/dl **Control group:** Insulin therapy only: once daily Lantus Solostar with a max dose of 60 units per day	**Primary endpoint:** • Reduction in HbA1c levels at 30 weeks **Secondary safety endpoint:** • Risk of adverse effects (namely hypoglycemia and gastrointestinal effects)	**Primary endpoint:** • Soliqua showed greater reduction in HbA1c from baseline compared to insulin glargine alone. • Soliqua reduction in HbA1c: -1.1% • Insulin glargine mean reduction in HbA1c: -0.06% • Soliqua mean final HbA1c: 6.9% • Insulin glargine mean final HbA1c: 7.5% **Secondary safety endpoint:** • Soliqua: Mean body weight decreased by 0.7 kg • Insulin glargine: Mean body weight increased by 0.7 kg • Documented symptomatic hypoglycemia events were comparable between the groups. • Mild GI adverse events: very low but more frequent with Soliqua **Overall conclusion:** Soliqua achieves greater reduction in HbA1c than insulin glargine alone. Mean body weight was decreased. Hypoglycemia incidents were comparable between the groups, and there was a slightly higher incidence of GI adverse events with Soliqua than with insulin glargine alone.

Conclusion:[1,2,3]

The clinical studies above along with other studies have demonstrated that Soliqua achieves significantly greater reductions in HbA1c compared to either insulin glargine or lixisenatide alone. Soliqua has been shown to be effective as both a monotherapy and in combination with up to two oral glucose-lowering agents. Both of the above clinical trials demonstrated no significant increase in adverse effects in Soliqua compared to either monocomponent. Additionally, Soliqua has the added benefit of showing significant weight loss compared to insulin glargine alone, which typically causes weight gain. No increases in hypoglycemic events were seen with Soliqua compared to insulin glargine alone.

- Benefits of LixiLan, a Titrable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial.[2]
  - Compared once daily insulin glargine/lixisenatide with insulin glargine alone and lixisenatide alone in patients previously taking metformin or other oral glucose-lowering agents
  - Mean HbA1c was lowest with insulin glargine/lixisenatide
  - A significantly higher percentage of patients receiving Soliqua reached HbA1c < 7% or <6.5%
  - Soliqua achieves more meaningful HbA1c reduction than either insulin or lixisenatide alone without causing weight gain. It has no increased risks of hypoglycemia compared to insulin alone
- Efficacy and Safety of LixiLan, a Titrable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial.[3]
  - Compared once daily insulin glargine/lixisenatide with insulin glargine alone and lixisenatide alone in patients inadequately controlled with basal insulin or up to two oral glucose-lowering agents
  - Soliqua showed greater reduction in HbA1c from baseline compared to insulin glargine alone.
  - Mean body weight was decreased with Soliqua and increased with insulin glargine alone.

Ongoing Clinical Trials:

- NCT02749890 – Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination (LixiLan) to Lixisenatide on Top of Oral Antidiabetic Drugs (OADs) With Type 2 Diabetes in Japan (LIXILAN-JPO1)
- NCT02787551 - Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC) Versus GLP-1 Receptor Agonist in Patients With Type 2 Diabetes, With a FRC Extension Period (LixiLan-G)

- NCT02752828 – Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination (LixiLan) to Insulin Glargine Alone on Top of Oral Anti-diabetic Drugs (OADs) With Type 2 Diabetes in Japan (LIXILAN JP-O2)
- NCT02752412 – Efficacy and Safety of LixiLan Versus Insulin Glargine Alone Both With Metformin in Japanese With Type 2 Diabetes Mellitus Inadequately Controlled on Basal Insulin and Oral Antidiabetic Drugs (LIXILAN JP-L)

Contraindications:[1] The use of Soliqua is contraindicated during hypoglycemic episodes. It is also contraindicated in patients with allergic hypersensitivity to insulin glargine, lixisenatide, or any of the product's excipients.

Warnings/Precautions:[1]
- Anaphylaxis and hypersensitivity reactions can occur with either component in Soliqua.
- Discontinue therapy promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed.
- Do not share prefilled pens between patients, even if the needle is changed.
- Hyperglycemia or hypoglycemia may occur with changes in dose or regimen. Adjustments must be performed under medical supervision.
- Overdose is possible due to medication errors. Soliqua contains two medications, and patients must always check the label before each injection.
- Life-threatening hypoglycemia can occur. Adjustments in other antidiabetic medications, physical activity, or meal pattern may require more frequent monitoring of blood glucose.
- Monitor renal function in patients with renal impairment and in patients with severe GI adverse reactions. Use is not recommended in end-stage renal disease.
- Patients may develop antibodies to insulin glargine and lixisenatide. Consider alternative therapy if patient does achieve proper glycemic control or experiences significant injection site or allergic reactions.
- Life-threatening hypokalemia may occur. Monitor patients at risk for hypokalemia.
- Concurrent use with thiazolidinediones (TZDs) may cause fluid retention and heart failure.
- Studies have not shown macrovascular risk reduction with Soliqua.
- Disease-related concerns
    - Use is not recommended in patients with gastroparesis.
    - Frequent monitoring may be required for patients with renal impairment
    - Frequent monitoring may be required for patients with hepatic impairment

Drug Interactions:[1]
- Drugs that affect glucose metabolism may require adjustment of Soliqua. Closely monitor blood glucose.
- The following antiadrenergic drugs may mask symptoms of hypoglycemia:
    - Beta blockers
    - Clonidine
    - Guanethidine
    - Reserpine
- Lixisenatide delays gastric emptying, which may impact absorption of oral medications. Oral contraceptives, acetaminophen, and antibiotics should be taken at least 1 hour prior to Soliqua administration.

Common Adverse Effects:[1,2,3]
- Hypoglycemia
- Allergic reactions
- Nausea
- Nasopharyngitis
- Diarrhea
- Upper respiratory tract infection
- Headache

Safety:[1,4]
- Dosed in insulin units, which may lead providers to mistakenly think that Soliqua contains only insulin and prescribe an additional GLP-1 agonist in addition to Soliqua
- Contains a lower dose of GLP-1 agonist than is currently approved for the single GLP-1 component
- Not indicated for treatment of Type 1 Diabetes or diabetic ketoacidosis (DKA)
- Has not been studied in patients with a history of unexplained pancreatitis; consider other therapies for these patients
- Not recommended for use in combination with another GLP-1 agonist or any other agents containing lixisenatide

Dosage/Administration:[1,5]

- Each prefilled Soliqua Solostar pen contains 100 units of insulin/mL and and 33 mcg lixisenatide/mL
- The minimum dose is 15 units of insulin
- Discontinue therapy with basal insulin or lixisenatide prior to therapy
- Inject subcutaneously in thigh, upper arm, or abdomen
- Prior to first injection
    - Remove pen from refrigerator at least 1 hour prior to injection
- Daily use of pen
    - Pull off the pen cap
    - Check to see that the medication is clear and almost colorless
    - Screw needle on and remove needle cap
    - Perform a safety test before each injection
        - Select 2 units by turning the dose selector
        - Press injection button all the way in until medication is visible at the tip of the needle
    - Inject once daily in the hour prior to the first meal of the day
        - Select the prescribed dose
        - Press injection button and hold for 2 seconds
    - Remove and throw away needle after each injection
    - Store pen at room temperature between uses

Special Drug Monitoring:[1]

- Diabetes mellitus monitoring: plasma glucose, electrolytes, HbA1c at least twice yearly in patients who have stable glycemic control and are meeting treatment goals or quarterly in patients how meeting treatment goals or with therapy change
- Potassium: monitor in patients at risk for hypokalemia
- Renal function
- Signs and symptoms of pancreatitis
- GI adverse effects: nausea, vomiting, diarrhea
- Signs and symptoms of hypersensitivity

Handling and Preparation:[1,5]

- Soliqua 100/33 pen should be stored in a refrigerator (2-8 degrees C) before first use.
    - Do not freeze. Protect from light. Discard after expiration date printed on the label.
- After first use, store at room temperature below 30 degrees C.
- Multiple dose pen:
    - Replace pen cap after each use to protect from light.
    - Discard pen 14 days after first use.
    - Remove the needle after each injection and store the pen without a needle attached. Use a new needle for each infection to prevent contamination.

Financial Impact:[6,7]

- According to the CDC, more than 29 million Americans are living with diabetes
    - Type 2 Diabetes makes up 90-95% of all diagnosed cases in the US
    - Seventh leading cause of death in the US
    - More than 20% of healthcare spending is for people with diagnosed diabetes
- No pharmacoeconomic studies found

Medication	WAC package pricing	AWP package pricing	AWP unit price
Soliqua (insulin glargine + lixisenatide) 3 ml 5 s	$635	$762	$50.80
Xultophy (insulin degludec + liraglutide) 3 ml 5 s	$953	$1143.82	$76.25
Basaglar Kwikpen (insulin glargine) 3 ml 5 s	$316.85	$380.22	$25.35
Trulicity (dulaglutide) 0.5 ml 4 s	$626	$751.20	$375.60

Victoza (liraglutide) 3 ml 3 s	$747.63	$897.16	$99.68

References:

1. Soliqua 100/33 [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S.; 2016.
2. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a Titrable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial. *Diabetes Care.* 2016;39(11):2026-2035. doi:10.2337/dc16-0917.
3. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and Safety of LixiLan, a Titrabile Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial. *Diabetes Care.* 2016;39(11):1972-1980. Doi10.2337/dc16-1495
4. ISMP Quarterly Action Agenda. Institute for Safe Medication Practices Website. https://www.ismp.org/newsletters/acutecare/ActionAgendas_PDF/ActionAgenda1701.pdf. Published January 27, 2017. Accessed April 1, 2017.
5. Soliqua 100/33: How to use. Sanofi. https://www.soliqua100-33.com/how-to-use-soliqua100-33. Published 2017. Updated 2017. Accessed April 17, 2017.
6. Diabetes. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/data/statistics/2014statisticsreport.html. Updated 2016. Accessed April 22, 2017.
7. Red Book Online [database online]. Ann Arbor, MI: Truven Health Analytics Inc. http:// www.micromedexsolutions.com. Updated 2017. Accessed January April 17, 2017.

Pharmacy &Therapeutics Committee Summary Review
Spinraza® (Nusinersen) – Biogen

Prepared by: Courtney Seekins, PharmD Candidate 2018 **Presentation Date:** July 6, 2017

Therapeutic Class[1]: Antisense Oligonucleotide **FDA Approval Date[2]:** December 23, 2016

FDA Indication[2]: For treatment of spinal muscular atrophy (SMA) in pediatric and adult patients

Comparable Formulary Products[3,4]: There are no other medications approved for SMA. Prior to approval of nusinersen, supportive therapy was the only form of treatment.

Proposed Designation and Rationale[2,3]

Recommendation: Non-preferred, Medical benefit ONLY

- Criteria for use: Previously approved via e-vote on 5/17/2017.
  - See posted policy with criteria: https://www.caresource.com/documents/spinraza-nusinersen-oh-med/
- Initial authorization: 6 months; Reauthorization: 12 months

Clinical Implications/Place in Therapy[2,4]:
The application for drug approval for nusinersen was grated fast track designation and priority review. However, the ENDEAR trial, which was the main basis for the rushed approval has not yet had full results published. Additional open-label students were uncontrolled lacking a control group but findings appeared generally supportive and similar to efficacy results seen in the ENDEAR trial. There are additional studies which are active and/or still recruiting patients.

Clinical Pharmacology[1]: It is an antisense oligonucleotide (ASO) used to treat SMA caused by mutations in chromosome 5q that leads to survival motor neuron (SMN) protein deficiency. It binds to a specific sequence in the intron downstream of exon 7 of the SMN2 messenger ribonucleic acid (mRNA) transcript and increases production of full-length SMN protein.

Notable Pharmacokinetics[1]:

Absorption:
- Following intrathecal administration, trough plasma concentrations of nusinersen were relatively low, compared to the trough CSF concentration
- Median plasma Tmax values ranged from 1.7 to 6.0 hours.
- Mean plasma Cmax and AUC values increased approximately dose-proportionally up to a dose of 12 mg

Distribution:
- Distributed within the peripheral and CNS tissues, such as skeletal muscle, liver and kidney

Metabolism:
- Metabolized via exonuclease (3'- and 5')-mediated hydrolysis and is not a substrate for, or inhibitor or inducer of CYP450 enzymes
- Half-life elimination: Terminal (mean range): CSF: 135 to 177 days; Plasma: 63 to 87 days
- Time to peak (median range): 1.7 to 6 hours

Excretion:
- Eliminated via urinary excretion

Efficacy[1]: (Study has not been officially published at this time)

Trial Design/ Population	Groups	Outcomes	Partial Results

ENDEAR Trial
Design: Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study
 	
Objective: To assess the clinical efficacy and safety of nusinersen administered intrathecally in patients with infantile-onset spinal muscular atrophy
	Population: Infants diagnosed with Spinal Muscular Atrophy born between 37 and 42 weeks (N=122)
	• Have survival motor neuron 2 (SMN2) copy number = 2
	• Body weight ≥ 3rd percentile for age
	• Be able to follow all study procedures
	• Reside within 9 hours ground travel distance from center
	Groups:
	• 2:1 randomization to two groups:
	  ○ Nusinersen 12mg/5mL intrathecal injection
	  ○ Sham injection
		Primary Outcome: To examine the clinical efficacy of nusinersen administered intrathecally to participants with infantile-onset SMA
		
		Secondary Outcome: To examine the safety and tolerability of nusinersen administered intrathecally to participants with infantile-onset SMA
			Efficacy analysis was conducted on patients who died, withdrew, or completed at least 183 days of treatment (N=82).
			
			Primary: 40% of patients in treatment group had a motor milestone response according to HINE Section 2 evaluation (p <0.0001) in comparison to 0% in the sham procedure
			
			No Secondary results have been published.

No other studies have results published at this time

*Additional open-label uncontrolled studies have been done in symptomatic patients who range in age from 30 days to 15 years at first dose and pre-symptomatic patients who range from 8 to 42 days at first dose.

- Both studies lacked a control group
- Patients in these studies had or were expected to develop Type 1, 2, or 3 SMA
- Findings appeared generally supportive of the efficacy results seen in the ENDEAR trial
    - Several patients achieved milestones such as ability to sit unassisted, stand, or walk despite the fact that this was not expected to happen
    - Milestones were maintained despite the fact that those milestones would have been expected to be lost
    - Patients survived to unexpected ages

Conclusion:

- The ENDEAR trial was the main basis for rushed approval for Nusinersen in treatment of SMA.
    - Full results of this study have still not been published.
- Many other studies being done on nusinersen are active and/or still recruiting patients
- Conclusion from ENDEAR trial and the partial results of ongoing studies:
    - The overall findings of the controlled trial in infantile-onset SMA and the open-label uncontrolled trials support the effectiveness of SPINRAZA across the range of SMA patients, and appear to support the early initiation of treatment with SPINRAZA.

Ongoing Clinical Trials[5]:

Active, not recruiting: A Study of Multiple Doses of Nusinersen Delivered to Infants with Genetically Diagnosed and Presymptomatic Spinal Muscluar Atrophy

Active, not recruiting: A Study to Assess the Safety and Tolerability of Nusinersen in Participants with Spinal Muscular Atrophy

Available: Expanded Access Program for Nusinersen in Participants with Infantile-onset (Consistent with Type 1) Spinal Muscular Atrophy

Enrolling by invitation: A Study for Participants with Spinal Muscular Atrophy who Previously Participated in Nusinersen Investigational Studies

Contraindications[1]: None

Warnings/Precautions[1]:

- Thrombocytopenia and coagulation abnormalities
    - Perform a platelet count and coagulation laboratory testing at baseline and prior to each administration of nusinersen and as clinically needed
- Renal Toxicity: Elevated urine protein
    - Conduct quantitative spot urine protein testing at baseline and prior to each dose of nusinersen
    - For urinary protein concentrations greater than 0.2 g/L, consider repeat testing and further evaluation

Drug Interactions[1]: None

Common Adverse Effects[1]:

- Lower respiratory infections (43%)
- Upper respiratory infections (39%)
- Constipation (30%)
- Teething (14%)
- Upper respiratory tract congestion (6%)
- Aspiration (5%)
- Ear infection (5%)
- Scoliosis (5%)

Safety:

- *Nusinersen (Spinraza ®) is not a Sound Alike Look Alike drug[6]*
- *Nusinersen does not have a REMs Program Requirement[7]*
- *Nusinersen is considered a high alert medication, according to ISMP, due to it being an intrathecal injection[8]*

Dosage/Administration[1]:

- Injection: 12mg/5 mL (2.4 mg/mL) nusinersen as a clear and colorless solution in a single-dose vial
    - Administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures
    - Initiate treatment with 4 loading doses:
        - The first 3 doses should be administered at 14-day intervals
        - The 4th loading dose should be administered 30 days after the 3rd dose
    - A maintenance dose should be administered once every 4 months thereafter

Special Drug Monitoring[1]:

- Conduct at baseline, prior to each dose of nusinersen and as clinically necessary:
    - Platelet count
    - Prothrombin time; activated partial thromboplastin time
    - Quantitative spot urine protein testing

Handling, Preparation and Administration[1]:

- Preparation:
    - Store medication in the carton in a refrigerator until time of use
    - Prior to administration, allow nusinersen to warm to room temperature prior to administration
    - Inspect medication for particulate matter and discoloration prior to administration
        - Do not administer nusinersen if visible particulates are observed or if the liquid in the vial is discolored
    - Withdraw 12 mg (5 mL) of nusinersen from the single-dose vial into a syringe and discard unused contents of the vial
    - Administer nusinersen within 4 hours of removal from the vial
- Administration:
    - Consider sedation as indicated by the clinical condition of the patient
    - Consider imaging techniques to guide intrathecal administration of nusinersen
    - Prior to administration, remove 5 mL of cerebrospinal fluid
    - Administer intrathecal bolus injection over 1 to 3 minutes using a spinal anesthesia needle
    - Do not administer in areas of the skin where there are signs of infection

Financial Impact[9]:

- *Commonality of disease drug is used to treat:*
    - SMA affects about 1 in 10,000 babies, and about 1 in every 50 Americans is a genetic carrier.
    - It can affect any race or gender
- *Acquisition cost and annual budget impact:*
    - WAC Package Price: $125,000
    - AWP Package Price: $150,000
    - The first year would require 6 treatments:
        - $150,000 x 6 = $900,000 in the first year
    - Following years with maintenance dosing:
        - $150,000 x 3 = $450,000 per year

Place in Therapy[3,4]:

- Only form of treatment for spinal muscular atrophy (SMA) in pediatric and adult patients

References:

1. Nusinersen (Spinraza) [prescribing information]. Research Triangle Park, NC: Biogen; December 2016.
2. U.S. Food and Drug Administration. Nusinersen (Spinraza). Updated December 2016. Accessed March 30, 2017. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm525780.htm
3. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: Diagnosis and management in a new therapeutic era. *Muscle Nerve*. 2015;51(2):157-167.
4. Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. *Ann Neurol*. 2016.
5. Nusinersen. Clinical Trials.gov Web site. clinicaltrials.gov. Updated 2017. Accessed March 30, 2017.
6. FDA and ISMP lists of look-alike drug names with recommended tall man letters. ISMP Web site. www.ismp.org. Updated 2016. Accessed March 30, 2017.
7. U.S. Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). Updated 2017. Accessed March 30, 2017.
8. Centers for Disease Control and Prevention (CDC). NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016. Accessed March 30, 2017.
9. Redbook. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Updated 2017. Accessed March 30, 2017.

CareSource

CNS: Anticonvulsants

Current PDL	Recommendations	Rationale	P&T Decision
Preferred **Acetazolamide** **Carbamazepine** (Tegretol) **Carbamazepine extended release** (Carbatrole, Epitol, Equetro) capsule, suspension, tablet, chewable tablet Clobazam (Onfi) - *OH and KY* o *Continuity of care* o *Previously approved for and currently using Aptiom, Banzel, Fycompa, Lyrica, Potiga or Vimpat* o *Diagnosis of seizures or epilepsy and 30 day trial of one of the following: gabapentin, lamotrigine (Lamictal), divalproex (Depakote), levetiracetam (Keppra), levetiracetam ER (Keppra XR), oxcarbazepine (Trileptal), carbamazepine (Carbatrol, Tegretol), Phenytoin (Dilantin), topiramate (Topamax), valproic acid (Depakene) or zonisamide* - *IN* o *No PA required for 32 mL/day (suspension), 8 tablets per day (10 mg) and 4 tablets per day (20 mg)* **Clonazepam** (Klonopin) tablet **Clorazepate** (Tranxene-T) **Diazepam rectal** gel (Diastat, Diastat Acudial, Diastat Pedi) **Diazepam (**Valium) concentrate, solution, tablet, vial **Divalproex sodium delayed release** (Depakote) **Divalproex sodium extended release** (Depakote ER) **Ethosuximide** (Zarontin) Ethotoin (Peganone) Ezogabine (Potiga) - *Continuity of care* - *Previously approved for and currently using Banzel, Lyrica, Onfi, Stavzor, or Vimpat* - *Diagnosis of seizures or epilepsy and 30 day trial of one of the following: gabapentin, lamotrigine (Lamictal), divalproex (Depakote), levetiracetam (Keppra), levetiracetam ER (Keppra XR), oxcarbazepine (Trileptal), carbamazepine (Carbatrol, Tegretol), Phenytoin (Dilantin), topiramate (Topamax), valproic acid (Depakene) or zonisamide* **Felbamate** (Felbatol) **Gabapentin capsules, tablets** (Neurontin) - *OH and KY* o *100 mg = 1080 caps per month* o *300 mg = 360 caps per month*	Potiga - Add Aptiom and Fycompa to approved/currently using - Remove Stavzor (discontinued) Lyrica - Add Aptiom to approved/currently using - Remove Stavzor (discontinued) Briviact - Add Aptiom to approved/currently using Gabapentin - No QL on PDL for IN	Update Briviact, Lyrica, and Potiga for consistently across brand name agents. Update gabapentin on PDL for clarity on coverage.	Approved

CNS: Anticonvulsants

- *400 mg = 270 caps per month*
- *600 mg = 180 tabs per month*
- *800 mg = 120 tabs per month*

- *IN : 360 tabs per month*

Gabapentin solution (Neurontin)

Lacosamide (Vimpat)

- *Continuity of care*
- *Previously approved for and currently using Aptiom, Banzel, Fycompa, Lyrica, Onfi, or Potiga*
- *Age 17 years and older, diagnosis of seizures or epilepsy and 30 day trial of one of the following: gabapentin, lamotrigine (Lamictal), divalproex (Depakote), levetiracetam (Keppra), levetiracetam ER (Keppra XR), oxcarbazepine (Trileptal), carbamazepine (Carbatrol, Tegretol), Phenytoin (Dilantin), topiramate (Topamax), valproic acid (Depakene) or zonisamide*

Lamotrigine (Lamictal) tablet, chewable tablet

Levetiracetam (Keppra)

Levetiracetam extended-release (Keppra)

Levetiracetam inj (Keppra)

Lorazepam Intensol concentrate

Lorazepam (Ativan) tablet, vial

Methsuximide (Celontin)

Oxcarbazepine (Trileptal)

Perampanel (Fycompa)

- *Continuity of care*
- *Previously approved for and currently using Aptiom, Banzel, Lyrica, Onfi, Potiga,, or Vimpat*
- *30 day trial of one of the following: gabapentin, lamotrigine (Lamictal), divalproex (Depakote), levetiracetam (Keppra), levetiracetam ER (Keppra XR), oxcarbazepine (Trileptal), carbamazepine (Carbatrol, Tegretol), Phenytoin (Dilantin), topiramate (Topamax), valproic acid (Depakene) or zonisamide*

Phenobarbital

Phenytoin (Dilantin Infatabs)

Phenytoin sodium extended (Dilantin, Phenytek)

Pregabalin (Lyrica) capsule

- *OH and KY*
  - *Continuity of care (for new member must meet below diagnoses)*
  - *Diagnosis of fibromyalgia, neuropathy, neuralgia, sciatica*
    - *30 day trial of gabapentin at accepted daily doses of 1200 mg to 2400 mg, amitriptyline, or duloxetine (must include quantity/days)*

CNS: Anticonvulsants

- *Diagnosis of seizure or epilepsy*
  - *30 day trial of one of the following: gabapentin, lamotrigine (Lamictal), divalproex (Depakote), levetiracetam (Keppra), levetiracetam er (Keppra XR), oxcarbazepine (Trileptal), carbamazepine (Carbatrol, Tegretol), Phenytoin (Dilantin), topiramate (Topamax), valproic acid (Depakene) or zonisamide*
  - *OR, previously approved for and currently using Banzel, Onfi, Potiga, Stavzor, or VImpat*
- *IN: Preferred in IN. No PA required.*

Primidone (Mysoline)
Rufinamide (Banzel)
- *Previously approved for and currently using Aptiom, Fycompa, Lyrica, Onfi, Potiga,, or Vimpat*
- *Diagnosis of seizure or epilepsy and 30 day trial of one of the following: gabapentin, lamotrigine (Lamictal), divalproex (Depakote), levetiracetam (Keppra), levetiracetam er (Keppra XR), oxcarbazepine (Trileptal), carbamazepine (Carbatrol, Tegretol), Phenytoin (Dilantin), topiramate (Topamax), valproic acid (Depakene) or zonisamide*

Tiagabine (Gabitril)
Topiramate (Topamax) sprinkle capsule, tablet
Valproic Acid (Depakene)
Zonisamide (Zonegran)

Non-preferred
Brivaracetam (Briviact) solution, intravenous solution, tablet
- *Continuity of care*
- *Previously approved for and currently using Banzel, Fycompa, Lyrica, Onfi, Potiga or Vimpat*
- *Diagnosis of seizures or epilepsy and 30 day trial of one of the following: gabapentin, lamotrigine (Lamictal), divalproex (Depakote), levetiracetam (Keppra), levetiracetam er (Keppra XR), oxcarbazepine (Trileptal), carbamazepine (Carbatrol, Tegretol), Phenytoin (Dilantin), topiramate (Topamax), valproic acid (Depakene) or zonisamide*

Clonazepam (Klonopin) ODT
- *OH and KY*
  - *Continuity of care*
  - *If fax states for use during seizures*
  - *If fax states inability to swallow*

CNS: Anticonvulsants

- *OR, clinical reason (OH MCD only) supported by chart notes why after a 30 day trial that clonazepam tablets cannot be used* - *IN* - *Preferred in IN. No PA required for 3 tablets/day* Eslicarbazepine (Aptiom) tablet - *Continuity of care* - *Previously approved for and currently using Banzel, Fycompa, Lyrica, Onfi, Potiga or Vimpat* - *Diagnosis of seizures or epilepsy and 30 day trial of one of the following: gabapentin, lamotrigine (Lamictal), divalproex (Depakote), levetiracetam (Keppra), levetiracetam er (Keppra XR), oxcarbazepine (Trileptal), carbamazepine (Carbatrol, Tegretol), Phenytoin (Dilantin), topiramate (Topamax), valproic acid (Depakene) or zonisamide* Hyoscyamine, atropine, scopolamine, phenobarbital (B-Donna, Donnatal, Donnatal Extentabs, Phenohytro) elixir, tablet, ER tablet - *30 day trial of phenobarbital 16.2 mg and hyoscyamine 0.125mg or 0.375 mg tablet taken separately at the same time* **Lamotrigine ODT** tablet and Starter Kit - *OH and KY* - *ODT tablet:* - *Diagnosis of seizures/epilepsy and 30 day trial of lamotrigine tablet* - *ODT Starter Kit* - *Diagnosis of seizures and clinical reason (OH MCD only) supported by chart notes why after a trial of lamotrigine tablets THEN lamotrigine ODT tablets cannot be used* - *IN* - *Preferred in IN. No PA required* **Lamotrigine ER** - *OH and KY* - *Diagnosis of seizures/epilepsy OR 30 day trial of lamotrigine tablet* - *QL = 30 tablets per 30 days* - *IN* - *Preferred in IN. No PA required* Levetiracetam (Spritam) disintegrating tablet - 30 day trial of levetiracetam solution Oxcarbazepine ER (Oxtellar XR) - *OH and KY* - *Continuity of care*			

CNS: Anticonvulsants

○ *Clinical reason (OH MCD only) supported by chart notes why after a 30 day trial oxcarbazepine (Triletpal) cannot be used* - *IN* ○ *Preferred in IN. No PA required* Pregabalin (Lyrica) solution - *OH and KY* ○ *Continuity of care (for new member must meet below diagnoses)* ○ *Diagnosis of fibromyalgia, neuropathy, neuralgia, sciatica* ▪ *30 day trial of gabapentin at accepted daily doses of 1200 mg to 2400 mg, amitriptyline, or duloxetine (must include quantity/days)* ○ *Diagnosis of seizure or epilepsy* ▪ *30 day trial of one of the following: gabapentin, lamotrigine (Lamictal), divalproex (Depakote), levetiracetam (Keppra), levetiracetam er (Keppra XR), oxcarbazepine (Trileptal), carbamazepine (Carbatrol, Tegretol), Phenytoin (Dilantin), topiramate (Topamax), valproic acid (Depakene) or zonisamide* ▪ *OR, previously approved for and currently using Banzel, Onfi, Potiga, Stavzor, or Vimpat* - *IN* ○ *Preferred in IN. No PA required* Rufinamide (Banzel) suspension - *Clinical reason (IN and OH MCD only) supported by chart notes why after a 30 day trial that Banzel tablet cannot be used* **Topiramate extended-release** (Qudexy XR) sprinkle capsule - *OH and KY* ○ *Diagnosis of seizure AND clinical reason (OH MCD only) why after a 30 day trial that topiramate IR tablets or capsules cannot be used* ○ *OR, diagnosis of migraine prophylaxis (age 12 and older) and clinical reason (OH MCD only) why after a 30 day trial that topiramate IR cannot be used (maximum dose of 100 mg per day)* - *IN* ○ *Preferred in IN. No PA required for 2 capsules/day* Topiramate extended-release (Trokendi) capsule - *OH and KY* ○ *Diagnosis of seizure AND clinical reason (OH MCD only) why after a 30 day trial that topiramate ER capsules cannot be used*			

CNS: Anticonvulsants			
o *OR, diagnosis of migraine prophylaxis (age 12 and older) and clinical reason (OH MCD only) why after a 30 day trial that topiramate ER capsules cannot be used (maximum dose of 100 mg per day)* - *IN* o *Preferred in IN. No PA required for 2 capsules/day* Vigabatrin (Sabril) tablet, powder - *Diagnosis of infantile spasms for whom the potential benefits outweigh the risk of vision loss, age 1 month to 2 years, prescribed by a pediatric neurologist or under the recommendation of a pediatric neurologist* - *Documented diagnosis of refractory complex partial seizures, prescribed by a neurologist or under recommendation of neurologist, age 10 years or older, and documentation of failure of two alternative treatments for the control of the complex partial seizures*			

CNS: Antidementia

Current PDL	Recommendations	Rationale	P&T Decision
Preferred **Donepezil** (Aricept) – 5 and 10 mg - *IN: No PA for 1 tablet per day* **Galantamine** (Razadyne) tablet, solution - *IN: No PA required for 6 mL/day (solution) and 2 tablets/day (tablet)* **Galantamine extended release** (Razadyne ER) - *IN: No PA required for 1 capsule/day* **Memantine** (Namenda) - *IN: No PA required for 10 mL/day (solution) and 2 tablets/day (tablet)* **Rivastigmine** (Exelon) capsule - *IN: No PA required for 2 capsules/day* **Non-Preferred** **Donepezil** (Aricept) 23 mg tablet - *OH and KY* o *Trial of donepezil 5 or 10mg tablet* - *Preferred in IN. No PA required for 1 tablet/day* Memantine ER (Namenda XR) capsule, titration pack - *OH and KY* o *Clinical reason (OH MCD only) why cannot after 30 day trial that memantine tablets (or memantine titration pack)* - *IN* o *Preferred in IN. No PA required for 1 capsule per day or 1 titration pack/28 days* Memantine/Donepezil (Namzaric) - *OH and KY* o *90 day trial of Namenda, donepezil, galantamine, or rivastigmine* - *IN* o *Preferred in IN. No PA required for 1 capsule/day* **Rivastigmine** (Exelon) patch - *OH and KY* o *Clinical reason (OH MCD only) why rivastigmine tablets cannot be used after a 90 day trial* - *IN* o *Preferred in IN. No PA required for 1 patchy/day*	None		Approved

CNS: Antidepressants – Monoamine Oxidase Inhibitors (MAOIs)

Current PDL	Recommendations	Rationale	P&T Decision
Preferred **Selegiline** (Zelapar) tablet, capsule **Tranylcypromine** (Parnate) - *IN: Preferred in IN. No PA required for 6 tablets/day* **Non-preferred** **Phenelzine** (Nardil) tablet - *OH and KY* o *Continuity or care or trial of Parnate* - *IN* o *Preferred in IN. No PA required for 6 tablets/day* Selegiline (Emsam) patch - *OH and KY* o *A claim within the last 30 days* o *If previously approved and currently using Trintellix, Pristiq, Venlafaxine ER, Viibryd, Desvenlafasine ER, Khedezla, Fetzima, or Fluvoxamine ER* o *Or 30 day trails of 2 of the 3 following preferred formulary groups with one occurring within the last year* ▪ *Group-1: Generic SSRI (Escitalopram, Citalopram, Fluoxetine, Paroxetine, Fluvoxamine, Sertraline)* ▪ *Group-2: Generic SNRI (Venlafaxine Tablet, Venlafaxine ER Capsule Or Duloxetine (Cymbalta)* ▪ *Group-3: Bupropion XL Or SR (Wellbutrin SR Or XL)* - *IN* o *Preferred in IN. No PA required for 1 patch/day* Isocarboxazid (Marplan) - *OH and KY* o *Continuity or care or trial of Parnate* - *IN* o *Preferred in IN. No PA required for 3 tablets/day* Selegiline (Zelapar) ODT - *Continuity of care* - *An inability to swallow* - *OR, clinical reason (OH and IN MCD) supported by chart notes why selegiline tablets cannot be used after a 30 day trial*	None		Approved

CNS: Antidepressants – Selective Serotonin Reuptake Inhibitors (SSRIs)

Current PDL	Recommendations	Rationale	P&T Decision
Preferred **Citalopram** (Celexa) - *IN: No PA required for 600 mL/month (solution) and 30 tabs/month (tablet)* **Escitalopram** (Lexapro) - *IN: No PA required for 30 tabs/month (5 mg and 10 mg tablet) and 45 tablets/month (20 mg tablet)* **Fluoxetine** (Prozac) - *IN* o *Capsules: No PA required for 30 capsules/month (10 mg) 120 capsules/month (20 mg), 60 capsules/month (40 mg)* o *Solution: No PA required for 600 mL/month* o *Tablets: No PA required for 45 tablets/month (10 mg), 120 tablets/month (20 mg), 4 tabs/28 days (DR tablets)* **Fluvoxamine** (Luvox) tablet - *IN* o *ER Capsules: No PA required for 60 capsules/month* o *Tablets: No PA required for 30 tablets/month (25 mg, 50 mg), 90 tablets/month (100 mg)* **Paroxetine** (Paxil) - *IN* o *Suspension: No PA required for 1200 mL/month, age 18 and older* o *Tablets: No PA required for 30 tablets/month (10 mg, 20 mg), 60 tablets/month (30 mg, 40 mg), 30 tablets/month (ER tablet), age 18 and older* **Sertraline** (Zoloft) - *IN:* o *Concentrate: 300 mL/month* o *Tablets: No PA required for 60 tablets/month (25 mg, 50 mg), 90 tablets/month (100 mg)* **Non-Preferred** Fluoxetine PMDD (Sarafem) tablet - *OH and KY* o *Clinical reason why fluoxetine capsule cannot be used* - *IN* o *Preferred in IN. No PA required for 1 tablet/day (10 mg) and 4 tablets/day (20 mg)*	None		Approved

CNS: Antidepressants – Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluvoxamine SR (Luvox CR) capsule
- *OH and KY*
  o *A claim within the last 30 days*
  o *If previously approved and currently using Trintellix, Pristiq, Venlafaxine ER, Viibryd, Desvenlafasine ER, Khedezla, Fetzima, or Fluvoxamine ER*
  o *Or 30 day trails of 2 of the 3 following preferred formulary groups with one occurring within the last year*
  ▪ *Group-1: Generic SSRI (Escitalopram, Citalopram, Fluoxetine, Paroxetine, Fluvoxamine, Sertraline)*
  ▪ *Group-2: Generic SNRI (Venlafaxine Tablet, Venlafaxine ER Capsule Or Duloxetine (Cymbalta)*
  ▪ *Group-3: Bupropion XL Or SR (Wellbutrin SR Or XL)*
- *IN*
  o *Preferred in IN. No Pa required for 2 capsules/day*
Paroxetine CR (Paxil CR, Pexeva) tablet
- *OH and KY*
  o *Clinical reason (OH MCD only) supported by chart notes why non-CR paroxetine cannot be used*
- *IN*
  o *Preferred in IN.* No PA required for 1 tablet/day, age 18 and older			

CNS: Antidepressants – Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Current PDL	Recommendations	Rationale	P&T Decision
Preferred **Duloxetine delayed release** (Cymbalta) - *IN: No PA required for 60 capsules/month.* **Venlafaxine** tablets - *IN: No PA required for 90 tablets//month.* **Venlafaxine extended release** (Effexor XR) capsule - *IN: No PA required for 30 capsules/month (37.5 mg), 90 capsules/month (75 mg), 60 capsules/month (150 mg)* **Non-preferred** **Desvenlafaxine** (Pristiq) ER tablet - *OH and KY* o *Ages 8-11: A claim within the last 30 days OR if previously approved by CareSource and currently using Trintellix, Pristiq, Venlafaxine ER, Viibryd, Desvenlafasine ER, Khedezla, Fetzima, or Fluvoxamine ER OR 30 day trial of fluoxetine within the last year* o *Ages 12-17: A claim within the last 30 days OR if previously approved by CareSource and currently using Trintellix, Pristiq, Venlafaxine ER, Viibryd, Desvenlafasine ER, Khedezla, Fetzima, or Fluvoxamine ER OR 30 day trial of fluoxetine within the last year* o *Age 18 or older: A claim within the last 30 days OR if previously approved by CareSource and currently using Trintellix, Pristiq, Venlafaxine ER, Viibryd, Desvenlafasine ER, Khedezla, Fetzima, or Fluvoxamine ER OR 30 day trial of 2 of the 3 following preferred formulary groups with one occurring within the least year* ▪ *Group-1: Generic SSRI (Escitalopram, Citalopram, Fluoxetine, Paroxetine, Fluvoxamine, Sertraline)* ▪ *Group-2: Generic SNRI (Venlafaxine Tablet, Venlafaxine ER Capsule Or Duloxetine (Cymbalta)* ▪ *Group-3: Bupropion XL Or SR (Wellbutrin SR Or XL)* - *IN* o *Preferred in IN. No PA required for 1 tablet/day (50 mg) and 2 tablets/day (100 mg)*	None		Approved

CNS: Antidepressants – Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Desvenlafaxine (Khedezla) extended-release tablet
- *OH and KY*
  - *Age 18 or older: A claim within the last 30 days OR if previously approved by CareSource and currently using Trintellix, Pristiq, Venlafaxine ER, Viibryd, Desvenlafasine ER, Khedezla, Fetzima, or Fluvoxamine ER OR 30 day trial of 2 of the 3 following preferred formulary groups with one occurring within the least year*
    - *Group-1: Generic SSRI (Escitalopram, Citalopram, Fluoxetine, Paroxetine, Fluvoxamine, Sertraline)*
    - *Group-2: Generic SNRI (Venlafaxine Tablet, Venlafaxine ER Capsule Or Duloxetine (Cymbalta)*
    - *Group-3: Bupropion XL Or SR (Wellbutrin SR Or XL)*
- *IN*
  - *Preferred in IN. No PA required for 1 tablet/day (50 mg) and 2 tablets/day (100 mg)*

Levomilnacipran (Fetzima) capsule
- *OH and KY*
  - *Age 18 or older: A claim within the last 30 days OR if previously approved by CareSource and currently using Trintellix, Pristiq, Venlafaxine ER, Viibryd, Desvenlafasine ER, Khedezla, Fetzima, or Fluvoxamine ER OR 30 day trial of 2 of the 3 following preferred formulary groups with one occurring within the least year*
    - *Group-1: Generic SSRI (Escitalopram, Citalopram, Fluoxetine, Paroxetine, Fluvoxamine, Sertraline)*
    - *Group-2: Generic SNRI (Venlafaxine Tablet, Venlafaxine ER Capsule Or Duloxetine (Cymbalta)*
    - *Group-3: Bupropion XL Or SR (Wellbutrin SR Or XL)*
- *IN*
  - *Preferred in IN. No PA required for 1 capsule/day*

Venlafaxine extended-release tablet
- *OH and KY*
  - *Clinical reason (OH MCD only) supported by chart notes why after a 30 day trial that venlafaxine ER capsule (37.5 mg, 75 mg, 150 mg) cannot be used*
  - *For 225 mg tablet, approve with the following note – Approved due to unique dosing and no comparable capsule strength*
- *IN*
  - *Preferred in IN. No PA required for 1 tablet/day (37.5 mg and 225 mg), 3 tablets/day (75 mg), and 2 tablets/day (150 mg)*

CNS: Antidepressants – Tricyclic Antidepressants (TCAs)

Current PDL	Recommendations	Rationale	P&T Decision
Preferred **Amitriptyline** (Elavil) - *IN: No PA required for 90 tablets/month.* **Amoxapine** - *IN: No PA required for 60 tablets/month (25 mg, 150 mg), 120 tablets/month (50 mg, 100 mg)* **Clomipramine** (Anafranil) capsule - *IN: No PA required for 60 capsules/month (25 mg), 150 capsules/month (50 mg), and 90 capsules/month (75 mg)* **Desipramine** (Norpramin) - *IN: No PA required for 120 tablets/month (25 mg, 50 mg, 75 mg, 150 mg), 90 tablets/month (100 mg)* **Doxepin** - *IN:* o *Capsules: No PA required for 120 capsules/month (10 mg), 60 capsules/month (25 mg, 50 mg, 75 mg, 100, 150 mg)* o *Concentrate: No PA required for 900 mL/month* **Imipramine** (Tofranil) - *IN:* o *Imipramine HCl Tablets: No PA required for 60 tablets/month (10 mg), 30 tablets/month (25 mg), 180 tablets/month (50 mg)* o *Imipramine pamoate Capsules: No PA required for 30 capsules/month (75 mg), 90 capsules/month (100 mg), 60 capsules/month (125 mg, 150 mg)* **Nortriptyline** (Pamelor) - *IN* o *Capsules: No PA required for 120 capsules/month (10 mg, 25 mg), 90 capsules/month (50 mg), 60 capsules/month (75 mg)* o *Solution: No PA required for 600 mL/month* **Protriptyline** (Vivactil) tablet - *IN: No PA required for 120 tablets/month* **Trimipramine** (Surmontil) - *IN: No PA required for 30 capsules/month (25 mg, 50 mg) and 90 capsules/month (100 mg)* ***Tricyclic Antidepressant/Benzodiazepine Combination*** **Chlordiazepoxide/Amitriptyline**	None		Approved

CNS: Antidepressants - Miscellaneous

Current PDL	Recommendations	Rationale	P&T Decision
Preferred **Bupropion** - *IN: No PA required for 120 tablets/month* **Bupropion extended release** (Wellbutrin SR) - *IN: No PA required for 60 tablets/month* **Bupropion extended release** (Wellbutrin XL) - *OH and KY: No PA required for 30 tablets/month* - *IN: No PA required for 30 tablets/month* **Maprotiline** tablet - *IN: No PA required for 90 tablets/month* **Mirtazapine** (Remeron) - *IN: No PA required for 30 tablets/month* **Nefazodone** tablet - *OH and KY* o *50 mg = 360 tablets/month* o *100 mg = 180 tablets/month* o *150 mg = 120 tablets/month* o *200 mg = 90 tablets/month* o *250 mg = 60 tablets/month* - *IN: No PA required for 60 tablets/month* **Trazodone** (Desyrel) 50 mg, 150 mg, 150 mg - *IN: No PA required for 60 tablets/month (50 mg), 90 tablets/month (100 mg, 150 mg)* **Non-Preferred** Bupropion (Aplenzin) extended-release tablet - *OH and KY* o *Clinical reason (OH MCD only) supported by chart notes why after 90 day trial that bupropion XL (Wellbutrin XL) 150 mg or 300 mg tablet cannot be used* - *IN* o *Preferred in IN. No PA required for 30 tablets/month* Bupropion (Forfivo) extended-release 450mg tablet - *OH and KY* o *Clinical reason (OH MCD only) supported by chart notes why after 90 day trial that bupropion XL 150 mg (3 tablets) or buproprion XL 150 mg AND 300 mg tablet together* - *IN*	Maprotiline - Not on PDL (OH/KY) Oleptro - Not on PDL (IN) Trintellix - Lists itself as trial agent (duplicative) Viibryd - Lists itself as trial agent (duplicative)	Update Trintellix and Viibryd for clarity for criteria requirements. Update Maprotiline and Oleptro on PDL for clarity on coverage.	Approved

CNS: Antidepressants - Miscellaneous

○ *Preferred in IN. No PA required for 30 tablets/month* Vortioxetine (Trintellix) tablet - *OH and KY* ○ *A claim within the last 30 days* ○ *If previously approved and currently using Trintellix, Pristiq, Venlafaxine ER, Viibryd, Desvenlafasine ER, Khedezla, Fetzima, or Fluvoxamine ER* ○ *Or 30 day trails of 2 of the 3 following preferred formulary groups with one occurring within the last year* ▪ *Group-1: Generic SSRI (Escitalopram, Citalopram, Fluoxetine, Paroxetine, Fluvoxamine, Sertraline)* ▪ *Group-2: Generic SNRI (Venlafaxine Tablet, Venlafaxine ER Capsule Or Duloxetine (Cymbalta)* ▪ *Group-3: Bupropion XL Or SR (Wellbutrin SR Or XL)* - *IN: Preferred in IN. No PA required for 30 tablets per month or 1 Viibryd kit per month)* Vilazodone (Viibryd) tablet - *OH and KY* ○ *A claim within the last 30 days* ○ *If previously approved and currently using Trintellix, Pristiq, Venlafaxine ER, Viibryd, Desvenlafasine ER, Khedezla, Fetzima, or Fluvoxamine ER* ○ *Or 30 day trails of 2 of the 3 following preferred formulary groups with one occurring within the last year* ▪ *Group-1: Generic SSRI (Escitalopram, Citalopram, Fluoxetine, Paroxetine, Fluvoxamine, Sertraline)* ▪ *Group-2: Generic SNRI (Venlafaxine Tablet, Venlafaxine ER Capsule Or Duloxetine (Cymbalta)* ▪ *Group-3: Bupropion XL Or SR (Wellbutrin SR Or XL)* - *IN: Preferred in IN. No PA required for 30 tablets per month.* Trazodone 300 mg tablet - *OH and KY* ○ *Clinical reason (OH MCD only) supported by char notes why after a trial that trazodone 150 mg (using 2 tablets to equal 300 mg) cannot be used* - *IN: Preferred in IN. NO PA required for 60 tablets/month.* Trazodone (Oleptro ER) tablet - *OH and KY*			

CNS: Antidepressants - Miscellaneous			
○ *Clinical reason (OH MCD only) supported by char notes why after a trial that trazodone IR cannot be used* - *IN: Preferred in IN. No PA required for 1.5 tablets/day (150 mg) and 1 tablet/day (300 mg)*			