Shortages

Amphetamine salt combos:

Current shortage, available to be ordered on allocation on M&D.

Lorazepam injection:

Current shortage due to manufacturing delays and increased demand. Still available to be ordered on allocation on M&D.

Sterile water for injection:

Current shortage due to increased demand. Still available to be ordered on allocation.

Rifampin:

Shortage due to discontinuation of manufacture of the drug by Akorn Pharmaceuticals, available to order on allocation.

Epinephrine Auto-Injector:

Current shortage, still available to be ordered on allocation.

Ozempic (semagltide):

Current shortage due to intermittent supply disruption which will continue through November 2022. Still available to be ordered on allocation.

Recalls

Magnesium Citrate Oral Solution:

Worldwide recall of some brands of magnesium citrate due to potential gluconacetobacter liquefaciens contamination.

Milk of Magnesia:

Nationwide recall of Major brand magnesium hydroxide/aluminum hydroxide/simethicone oral suspension due to microbial contamination.

Safety-related Labeling Changes

Amoxicillin/clavulanate potassium (Augmentin):

FDA added a section on "Severe Cutaneous Adverse Reactions (SCAR) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). Patients should be advised about the possible signs and symptoms of serious skin adverse effects and instructed to stop taking immediately at the first sign of skin issues.

News Briefs

The following information was shared with the committee members:

FDA Approves 'Rapid-Acting' Oral Drug for Major Depression

Medscape (8/22/22) reports "The US Food and Drug Administration (FDA) has approved the first oral *N*-methyl *D*-aspartate (NMDA) receptor antagonist for the treatment of major depressive disorder (MDD) in adults… *Auvelity* (Axsome Therapeutics) is a proprietary extended-release oral tablet containing dextromethorphan (45 mg) and bupropion (105 mg)." In addition to the antidepressant activity, buproprion also increases bioavailability of dextromethorphan through CYP2D6 inhibition. "It is the first and only rapid-acting oral medicine approved for the treatment of MDD with labeling of statistically significant antidepressant efficacy compared to placebo starting at one week," the company said in a news release… Axsome said it expects to launch the new oral medication in the fourth quarter of this year.

Positive Phase 3 Data for Lecanemab in Early Alzheimer's

Medscape (9/28/2022) reports "Lecanemab (Eisai/Biogen), an investigational amyloid-clearing monoclonal antibody, reduced cognitive decline by 27% compared to placebo and decreased amyloid levels in the brain of adults enrolled in a phase 3 trial. The Clarity AD trial included 1795 adults with early AD and confirmed amyloid pathology in the brain. Treatment consisted of lecanemab 10 mg/kg biweekly or matching placebo." Statistically significant differences in cognitive decline could be seen as early as 6 months. According to a press release, "in July 2022, the U.S. Food and Drug Administration (FDA) accepted Eisai's Biologics License Application (BLA) for lecanemab under the accelerated approval pathway and granted Priority Review. The Prescription Drugs User Fee Act action date (PDUFA) is set for January 6, 2023.

Open Forum

No items

Next Meeting Date

The next meeting is scheduled for January 27, 2023.

Adjourn

There being no further business, the meeting was adjourned at 2:44 p.m.

Approved: *David Moron*

David Moron, MD, Chairman

Minutes Prepared by:
Tonya Barrios, PhTR
Reviewed by:
Kasey L. Pena, PharmD

Appendix A

Ginkgo biloba L.

Botanical name: Ginkgo biloba L.
Family: Ginkgoaceae
Genus: Ginkgo
Plant part: Leaf
Common names: Fossil tree; Kew tree; Japanese silver apricot; Maidenhair tree

Classification

Central nervous system agent, miscellaneous

Pharmacology

Ginkgo biloba has two primary active ingredients at varying concentrations: terpene lactones (which most notably include ginkgolides and diterpenes) and ginkgo flavone glycosides (which most notably contain ginkgetin, bilobetin, and sciadopitysin). Most of the studies that investigate the effect of ginkgo extract often use the standardized extract of Ginkgo biloba (EGb) 761.

Ginkgo biloba extract has been shown to affect several neurotransmitter pathways and brain structures, mostly in animal studies. EGb761 limits stress-induced corticosterone hypersecretion by reducing the number of adrenal peripheral benzodiazepine receptors in rats. Ginkgo extract appears to have reversible inhibitory effects on rat brain monoamine oxidase by inhibiting the uptake of serotonin and dopamine. EGb761 also has modest inhibitory activities on anticholinesterase, hence increasing cholinergic transmission in the brain.

Several studies have suggested the neuroprotective effects of Ginkgo biloba extract. Long-term use of EGb761 appears to improve the short-term memory of middle-aged rats likely by reducing free radical production in the prefrontal cortex. It also protects against age-related changes in the mouse hippocampus. Additionally, Gingko biloba extract acts as a free radical scavenger and protects neurons from oxidative damage and apoptosis, which have been observed prominently in cerebral ischemia and Alzheimer disease.

The effects of ginkgo on the cardiovascular system are widely studied and mostly observed as protective. Ginkgo's role includes a regulator of metabolism, membrane stabilizer, and vasodilator. In the arterial endothelium, ginkgo biloba extract triggers the release of endogenous relaxing factors, such as endothelium-derived relaxing factor and prostacyclin. Under tissue-damaging inflammatory conditions such as ischemia, it can also moderate nitric oxide production and exert vasorelaxation properties. Also, terpene lactones are potent antagonists of the platelet-activating factor. Ginkgo extract also demonstrates fibrinolytic effects.

Black Box Warning

None

Indication

Ginkgo biloba may be helpful in reducing antipsychotic-induced tardive dyskinesia.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	60%+ absorbed GI
Excretion	Expiration, urine, feces

Dosage/Administration

240 mg/day

Use in Special Population

There is a lack of data regarding use in pregnancy and lactation; due to absent safety information, ginkgo should not be used in this population.

Contraindication

Caution should be exercised with ginkgo in patients with bleeding disorders or those who take anticoagulant drugs. The risk of spontaneous bleeding may be increased when ginkgo biloba extract is combined with nonsteroidal anti-inflammatory drugs (NSAIDs) and anticoagulants such as heparin or warfarin. Concomitant use of ginkgo with these agents should be avoided.

Precautions

- Bleeding disorders or anticoagulant use
- Seizure disorder

Adverse Effects

Severe adverse reactions are rare. Case reports describe headache, dizziness, and heart palpitations, as well as GI and dermatologic reactions.

Monitoring

Dietary supplements such as *Ginkgo biloba* do not require extensive pre-marketing approval from the U.S. Food and Drug Administration. On multiple occasions, nutritional supplements may contain several ingredients, and a discrepancy between labeled and actual ingredients or their amounts may occur. Physicians should be cautious regarding the safety or effectiveness of a dietary supplement.

Research has noted several interactions between *Ginkgo biloba* and other medications, as well as other dietary supplements.

EGb doses higher than the recommended ones may lead to a weak induction of the CYP2C19-mediated omeprazole 5-hydroxylation, and weak inhibition of the CYP3A4-mediated midazolam 1'-hydroxylation through the clinical implications of such findings are unclear. Overall, as long as the maximum consumption of EGb 761 does not exceed 240 mg daily, pharmacokinetic herb-drug interactions are at an acceptable limit.

As discussed above, physicians should be aware of the increased risk of bleeding when *Ginkgo biloba* was co-administered with other agents that have potential to increase bleeding (NSAIDs, antiplatelet, anticoagulant therapies, garlic, ginger, ginseng, etc.)

Due to its properties as monoamine oxidase inhibitors, ginkgo can precipitate serotonin syndrome in patients that are on other antidepressant medications.

Also, ginkgo has an elevating effect on blood sugar, so if patients have diabetes and take ginkgo, closely monitoring of blood glucose levels is recommended.

Interactions

The major components of ginkgo biloba preparations (terpenes, flavonol glycosides) do not significantly inhibit human cytochrome P450 isoforms in vitro. However, other components of ginkgo (flavonol aglycones, the bioflavonoid amentoflavone) do inhibit CYP1A2 and CYP3A4. The clinical importance of these potential interactions is uncertain.

Efficacy

OBJECTIVE: Free radicals may be involved in the pathogenesis of tardive dyskinesia (TD). Extract of Ginkgo biloba (EGb) is a potent antioxidant possessing free radical-scavenging activities. The aim of the study was to evaluate the efficacy of EGb-761, a standardized extract given in capsule form, in treating TD in schizophrenia patients.

METHOD: Inpatients with DSM-IV-diagnosed schizophrenia and TD (n = 157) in a mainland China Veterans Affairs psychiatric hospital were randomly assigned to 12 weeks of treatment with either EGb-761, 240 mg/d (n = 78) or a placebo (n = 79) in a double-blind manner. Primary outcome measures were (1) change from baseline in the Abnormal Involuntary Movement Scale (AIMS) score and (2) proportion of patients with a ≥30% reduction in their AIMS total score at week 12. Secondary outcome measures included the Positive and Negative Syndrome Scale (PANSS) and cognitive performance as measured by the Continuous Performance Test-37 Version and the 3-card Stroop task. Patients were recruited for the study between December 2006 and May 2007.

RESULTS: Of the 157 patients who were randomly assigned, 152 (96.8%) completed the study. EGb-761 treatment significantly decreased the AIMS total score in patients with TD compared to those who were given a placebo (2.13±1.75 vs -0.10±1.69;

P<.0001), with 40 (51.3%) and 4 (5.1%) patients achieving response in the EGb-761 and placebo treatment groups, respectively. There were no between-group differences in the PANSS total score or cognitive measures from baseline to week 12.

CONCLUSION: SEGb-761 appears to be an effective treatment for reducing the symptoms of TD in schizophrenia patients, and improvement may be mediated through the well-known antioxidant activity of this extract.

Dosage Forms/Cost (AWP)

40 mg, 60 mg, and 120 mg capsules

$4 to $12 per 100

Summary/Conclusion

Quality control of herbal and dietary supplements, including ginkgo biloba, is variable. Despite attempts by the US Food and Drug Administration (FDA) to improve regulation of quality and safety standards for dietary supplements, experts have criticized current standards as insufficient and enforcement activities as inadequate.

Recommendation

Ginkgo biloba should be added to the formulary.

References

1. https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-ginkgo-biloba-l-folium_en.pdf
2. Ginkgo biloba. In: Natural Medicines, Therapeutic Research Center Healthcare 2020 Available at: https://naturalmedicines.therapeuticresearch.com/ (Accessed on August 10, 2020).
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8901348/
4. https://www.ncbi.nlm.nih.gov/books/NBK541024/
5. US Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, MD, on the agency's new efforts to strengthen regulation of dietary supplements by modernizing and reforming FDA's oversight. Available at: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-new-efforts-strengthen-regulation-dietary (Accessed on August 08, 2020)
6. Weinmann S, Roll S, Schwarzbach C, Vauth C, Willich SN. Effects of *Ginkgo biloba* in dementia: systematic review and meta-analysis. *BMC Geriatr*. 2010;10:14.

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October 2022

Appendix B

Paliperidone palmitate extended-release injectable suspension (Invega Trinza®)

Classification[1]

Atypical antipsychotic

Pharmacology[1,2]

Paliperidone palmitate is hydrolyzed to paliperidone. Paliperidone is the major active metabolite of risperidone. Paliperidone is an antagonist at central dopamine Type 2 (D_2) and serotonin Type 2A ($5HT_{2A}$) receptors. It is also an antagonist at alpha-1 adrenergic, alpha-2 adrenergic, and H_1 histaminergic receptors.

Black Box Warning[1]

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Paliperidone palmitate is not approved for use in patients with dementia-related psychosis.

Indication[1]

Treatment of schizophrenia in patients after they have been adequately treated with 1-month paliperidone palmitate extended-release injectable suspension (1MPP/Invega Sustenna®) for at least 4 months.

Pharmacokinetics[1]

Pharmacokinetic Parameter	Details
Absorption	Paliperidone palmitate has extremely low water solubility. The 3-month formulation of paliperidone palmitate (3MPP) dissolves slowly after intramuscular (IM) injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. The release of the drug starts as early as day 1 and lasts for as long as 18 months.
Distribution	Following a single IM dose, the plasma concentrations gradually rise to reach maximum plasma concentrations at a median T_{max} of 30-33 days. IM injection in the deltoid muscle resulted in 11-12% higher C_{max} compared with IM injection in the gluteal muscle. The release profile and dosing regimen of paliperidone palmitate results in sustained therapeutic concentrations over 3 months. The apparent volume of distribution of paliperidone after 3MPP injection is 1960 L.

Pharmacokinetic Parameter	Details
Metabolism	Paliperidone is not extensively metabolized in the liver. Metabolic pathways identified in vivo include dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scissoion. The half-life of paliperidone following 273-819 mg doses of 3MPP administration ranged from 84-95 days after deltoid injections and 118-139 days after gluteal injections.
Excretion	59% of the dose is excreted unchanged in the urine.

Dosage/Administration[1]

3MPP is only to be used after 1-month paliperidone palmitate (1MPP) has been established as adequate treatment for at least four months. It is recommended that the last two doses of 1MPP be the same dosage strength before starting 3MPP. The dose of 3MPP should be given when the next 1MPP is scheduled. 3MPP may be given 7 days before or after the monthly time point of the next scheduled 1MPP.

Last dose of 1-month paliperidone palmitate (1MPP)	Initiate 3-month paliperidone palmitate (3MPP)
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Use in Special Populations[1]

Pregnancy: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal symptoms (EPS) and/or withdrawal symptoms following delivery. Available data from published epidemiological studies of pregnant women exposed to paliperidone have not established a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Paliperidone has been detected in plasma in adult subjects up to 18 months after a single dose of 3MPP and the clinical significance of 3MPP administered before pregnancy or anytime during pregnancy is not known. International schizophrenia guidelines generally recommend avoiding long-acting injectable (LAI) antipsychotics in pregnant women with unstable schizophrenia due to lack of flexibility in dosing.[3]

Lactation: Limited data from published literature report the presence of paliperidone in human breast milk. There is no information on the effects on the breastfed infant, or the effects on milk production. There are reports of sedation, failure to thrive,

jitteriness, and EPS in breastfed infants exposed to risperidone. Infants exposed to 3MPP through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and EPS (tremors and abnormal muscle movements).

Pediatric: Safety and effectiveness of 3MPP in patients less than 18 years of age have not been established. Use is not recommended in pediatric patients because of the potential longer duration of an adverse event compared to shorter-acting products. In clinical trials of oral paliperidone, there were notably higher incidences of dystonia, hyperkinesia, tremor, and parkinsonism in the adolescent population compared to the adult studies.

Geriatric: Clinical studies of 3MPP did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects.

Renal impairment: Not recommended in patients with moderate or severe renal impairment (CrCl < 50 mL/min). In patients with mild renal impairment (CrCl $\geq$50 mL/min to < 80 mL/min), the dose of 3MPP is based on the previous dose of the 1MPP.

Hepatic impairment: 3MPP has not been studied in patients with hepatic impairment. Based on oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment.

Contraindications[1]

Patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the 3MPP formulation.

Precautions[1]

- Increased mortality in elderly patients with dementia-related psychosis
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis
- Neuroleptic malignant syndrome
- QT prolongation
- Tardive dyskinesia
- Metabolic changes
- Falls
- Leukopenia, neutropenia, and agranulocytosis
- Hyperprolactinemia
- Potential for cognitive and motor impairment
- Seizures
- Dysphagia
- Priapism
- Disruption of body temperature regulation

Adverse Effects[1]

The most common adverse reactions from two phases of a clinical trial were injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia, and parkinsonism. In the open label phase (n=506 of 1MPP, followed by n=379 3MPP), these adverse reactions had an incidence of at least 5%. In the double-blind phase (n=160 of 3MPP) these adverse reactions had an incidence at least twice the incidence in the placebo group. The mean (SD) duration of exposure during the double-blind phase was 175 (90) days in the 3MPP group.

Extrapyramidal symptoms (EPS) assessed by incidence of rating scales in the above study are shown in the following table:

Symptom	**Open-label Phase**	**Double-blind Phase**	
Scale	1MPP +/- 3MPP (n=506)	Placebo (n=145)	3MPP (n=160)
Parkinsonism	6%	3%	6%
Akathisia	3%	1%	4%
Dyskinesia	1%	3%	3%
Use of anticholinergic medication	11%	9%	11%

Monitoring[2]

- Improvement in signs and symptoms of schizophrenia or schizoaffective disorder and need for continued treatment
- Personal and family history of obesity, diabetes, and cardiovascular disease: baseline and update annually
- CBC with differential: Frequently during the first few months of therapy for patients with a history of low WBC or ANC or drug-induced leukopenia or neutropenia
- Fasting blood glucose: Baseline, at week 12, then annually or more frequently in patients with risk factors for diabetes
- Fasting lipid profile: Baseline, at week 12, then every 5 years
- Renal function: In elderly patients
- Prolactin level: As clinically indicated
- Blood pressure: Baseline, at week 12, then annually or more frequently in patients with risk factors for hypertension
- Waist circumference: Baseline, then annually

- Weight and BMI: Baseline, at week 4, week 8, and week 12 after starting or changing doses, then quarterly
- Symptoms of hyperglycemia: During treatment
- Orthostatic vital signs: In patients predisposed to hypotension
- Tardive dyskinesia: Baseline, then annually; every 6 months in patients at higher risk
- Fall risk assessment: In high-risk patients (elderly, patients on long-term therapy)
- Symptoms of hyperprolactinemia: At each visit until stable, then annually

Interactions

Paliperidone palmitate is hydrolyzed to paliperidone, so drug interactions with oral paliperidone should be considered. The following classes of medications have clinically important drug interactions with 3MPP:

- Centrally acting drugs and alcohol: Use 3MPP with caution with other centrally acting drugs and/or alcohol.
- Drugs with potential to cause orthostatic hypotension: Monitor vital signs in patients vulnerable to hypotension.
- Strong inducers of CYP3A4 and P-gp (e.g., carbamazepine, rifampin): Strong CYP3A4 and P-gp inducers may decrease the exposure to paliperidone. Avoid using CYP3A4 and P-gp inducers during the 3-month dosing interval if possible. If these medications are necessary, considering managing the patient with oral paliperidone tablets.
- Levodopa and other dopamine agonists: Monitor and manage patient clinically.

Efficacy

Efficacy for schizophrenia was evaluated in a long-term double-blind, placebo-controlled, randomized-withdrawal trial designed to evaluate time to relapse involving adult subjects who met DSM-IV-TR criteria for schizophrenia.

Patients could enter the study if they were clinically stable (already on a LAI antipsychotic) or if they had acute symptoms. Patients received appropriate initiation doses of 1MPP depending on current clinical status and current medications.

There were three treatment periods in the study:

1. 17-week flexible-dose open-label period with the 1MPP. 506 patients entered this phase of the study. Patients had to be clinically stable at the end of this period before receiving 3MPP at the week 17 visit (PANSS total score < 70).
2. 12-week open-label treatment period with 3MPP. 379 patients received 3MPP. Patients had to remain clinically stable before entry into the next period.
3. Variable length double-blind treatment period. 305 stabilized patients from the 2nd treatment period were randomized 1:1 to receive 3MPP or placebo every 12 weeks. Patients who received 3MPP received the same dose of 3MPP that they received during the 2nd treatment period.

The primary efficacy variable was time to first relapse, which was defined as psychiatric hospitalization, > 25% increase or 10-point increase in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score > 5 (if the max baseline score was < 3) or > 6 (if the max baseline score was 5) on two consecutive assessments of the specific PANSS items.

A pre-planned interim analysis showed a statistically significantly longer time to relapse in patients treated with 3MPP compared to placebo, which resulted in the study ending early because of demonstrated efficacy.

Twenty-three percent (23%) of patients in the placebo group and 7.4% of patients in the 3MPP group experienced a relapse event. The median time to relapse in the placebo group was 274 days. The median time in the 3MPP group could not be estimated due to low percentage of subjects with relapse.

Dosage Forms/Cost (AWP)[4]

Dose of 3-month paliperidone palmitate	AWP
273 mg	$3,829.96
410 mg	$5,745.02
546 mg	$7,660.33
819 mg	$11,490.24

Invega Trinza does have a Patient Assistance Program (PAP).

Summary/Conclusion

Invega Trinza is the only long-acting injectable antipsychotic that is administered every 3 months. Patients must be stabilized on 1-month paliperidone palmitate (Invega Sustenna) for 4 months prior to receiving Invega Trinza. Invega Trinza is an expensive medication, but it has a PAP program for outpatient use.

Recommendation

Invega Trinza should be added to the formulary as a reserve drug with the criteria that it only be used in the outpatient setting for patients who have been stabilized on Invega Sustenna for at least 4 months prior to initiation.

References

1. Invega Trinza. Prescribing information. Janssen Pharmaceuticals, Inc; March 2022. Accessed September 20, 2022.

2. Paliperidone. IBM Micromedex. IBM Watson Health. Cambridge, MA. Available at http://www.micromedexsolutions.com. Accessed September 20, 2022.
3. Lefebvre A, Pouchon A, Bioulac S, Mallet J, Polosan M, Dondé C. Management of schizophrenia in women during the perinatal period: a synthesis of international recommendations. Expert Opin Pharmacother. Published online July 19, 2022:1-14. doi:10.1080/14656566.2022.2102421.
4. McKesson wholesaler pricing information accessed September 20, 2022.

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September 20, 2022

Appendix C

Semaglutide (Ozempic®, Wegovy®)

Classification

- Antidiabetic agent (Ozempic)
- Weight loss agent (Wegovy)

Pharmacology

Semaglutide is a human glucagon-like peptide 1 (GLP-1) receptor agonist (incretin mimetic). Semaglutide activates the GLP-1 receptor in pancreatic beta cells leading to glucose-dependent insulin release. It also decreases glucagon secretion, slows gastric emptying, and promotes satiety.

Indication

- Ozempic:
  - Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
  - Reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease
- Wegovy:
  - Chronic weight management in adults with BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 with hypertension, type 2 diabetes, or dyslipidemia

Black Box Warning

WARNING: RISK OF THYROID C-CELL TUMORS

In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether semaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

Semaglutide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of semaglutide and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with semaglutide.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Bioavailability = 89%; max concentration reached 1-3 days post dose; similar exposure with subcutaneous administration in abdomen, thigh, or upper arm
Distribution	Extensively bound to plasma albumin (> 99%)
Metabolism	Proteolytic cleavage of peptide backbone, beta-oxidation of the fatty acid sidechain
Excretion	Half-life ≈ 1 week; Urine (3% unchanged drug), feces

Dosage/Administration

Administer subcutaneously in the abdomen, thigh, or upper arm. Instruct patients to use a different injection site each week when injecting in the same body region.

Administer once weekly, on the same day each week, at any time of day, with or without meals.

Ozempic: Start with 0.25 mg once weekly for 4 weeks. The 0.25 mg dosage is intended for treatment initiation and is not effective for glycemic control. Weeks 5 through 8 = 0.5 mg once weekly. If additional glycemic control is needed, Weeks 9 through 12 = 1 mg once weekly. If additional glycemic control is needed, Week 13 and onward = 2 mg once weekly (maximum recommended dosage).

Wegovy: Start with 0.25 mg once weekly for 4 weeks. Weeks 5 through 8 = 0.5 mg once weekly. Weeks 9 through 12 = 1 mg once weekly. Weeks 13 through 16 = 1.7 mg once weekly. Week 17 and onward = 2.4 mg once weekly.

If patients do not tolerate the maintenance 2.4 mg once-weekly dose, the dose can be temporarily decreased to 1.7 mg once-weekly, for a maximum of 4 weeks. After 4 weeks, increase back to 2.4 mg once-weekly. Discontinue if the patient cannot tolerate the 2.4 mg dose.

Use in Special Population

Pregnancy: There are limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. OZEMPIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. Additionally, weight loss offers no benefit to a pregnant patient and may cause fetal harm. When a pregnancy is recognized, advise the pregnant patient of the risk to a fetus and discontinue WEGOVY.

Lactation: There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats, however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for semaglutide and any potential adverse effects on the breastfed infant from semaglutide or from the underlying maternal condition.

Females and Males of Reproductive Potential: Discontinue at least 2 months before a planned pregnancy because of the long half-life of semaglutide.

Pediatric Use: Safety and efficacy of semaglutide have not been established in pediatric patients.

Geriatric Use: In the pool of placebo- and active-controlled glycemic control trials, 744 (23.6%) of OZEMPIC-treated patients were 65 years of age and over and 102 OZEMPIC-treated patients (3.2%) were 75 years of age and over. In Sustain 6, the cardiovascular outcome trial, 788 (48.0%) of OZEMPIC-treated patients were 65 years of age and over and 157 OZEMPIC-treated patients (9.6%) were 75 years of age and over.

No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment: No dose adjustment of semaglutide is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed.

Hepatic Impairment: No dose adjustment of semaglutide is recommended for patients with hepatic impairment. In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed.

Contraindication

- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

- A prior serious hypersensitivity reaction to semaglutide or to any of the excipients in Ozempic or Wegovy. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with semaglutide.

Precautions

Risk of Thyroid C-Cell Tumors: In mice and rats, semaglutide caused a dose-dependent and treatment-duration dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether semaglutide causes thyroid C-celL tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

Semaglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of semaglutide and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with semaglutide. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values greater than 50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Acute Pancreatitis: Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including semaglutide. Acute pancreatitis was observed in patients treated with semaglutide in clinical trials. After initiation of semaglutide, observe patients carefully for signs and symptoms of acute pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting). If acute pancreatitis is suspected, semaglutide should promptly be discontinued and appropriate management should be initiated. If acute pancreatitis is confirmed, semaglutide should not be restarted.

Semaglutide has not been studied in patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on semaglutide.

Acute Gallbladder Disease: In WEGOVY randomized clinical trials, cholelithiasis was reported by 1.6% of WEGOVY-treated patients and 0.7% of placebo-treated patients. Cholecystitis was reported by 0.6% of WEGOVY-treated patients and 0.2% of placebo-treated patients. Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in WEGOVY-treated patients than in placebo-treated patients, even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Hypoglycemia: Semaglutide lowers blood glucose and can cause hypoglycemia.

In a trial of patients with type 2 diabetes and BMI greater than or equal to 27 kg/m2, hypoglycemia (defined as a plasma glucose less than 54 mg/dL) was reported in 6.2% of WEGOVY-treated patients versus 2.5% of placebo-treated patients. One episode of severe hypoglycemia (requiring the assistance of another person) was reported in one WEGOVY-treated patient versus no placebo-treated patients.

Patients with type 2 diabetes mellitus taking semaglutide in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Hypoglycemia has been observed in patients treated with semaglutide (OZEMPIC) at doses of 0.5 and 1 mg in combination with insulin. The addition of WEGOVY in patients treated with insulin has not been evaluated.

Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. When initiating semaglutide, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.

Acute Kidney Injury: There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which have in some cases required hemodialysis, in patients treated with semaglutide. Patients with renal impairment may be at greater risk of acute kidney injury, but some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhea, leading to volume depletion.

Monitor renal function when initiating or escalating doses of semaglutide in patients reporting severe adverse gastrointestinal reactions. Monitor renal function in patients with renal impairment reporting any adverse reactions that could lead to volume depletion.

Hypersensitivity: Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with semaglutide. If hypersensitivity reactions occur, discontinue use of semaglutide, treat promptly per standard of care, and

monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to semaglutide or any of the excipients in WEGOVY or OZEMPIC.

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with semaglutide.

Diabetic Retinopathy Complications in Patients with Type 2 Diabetes: In a trial of patients with type 2 diabetes and BMI greater than or equal to 27 kg/m 2, diabetic retinopathy was reported by 4.0% of WEGOVY-treated patients and 2.7% placebo-treated patients.

In a 2-year trial with OZEMPIC 0.5 mg and 1 mg once-weekly injection in patients with type 2 diabetes and high cardiovascular risk, diabetic retinopathy complications (which was a 4-component adjudicated endpoint) occurred in patients treated with OZEMPIC (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic 2 retinopathy at baseline (OZEMPIC 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (OZEMPIC 0.7%, placebo 0.4%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Heart rate increase: Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed in WEGOVY-treated patients compared to placebo in clinical trials. More patients treated with WEGOVY compared with placebo had maximum changes from baseline at any visit of 10 to 19 bpm (41% versus 34%, respectively) and 20 bpm or more (26% versus 16%, respectively).

Monitor heart rate at regular intervals consistent with usual clinical practice. Instruct patients to inform their healthcare providers of palpitations or feelings of a racing heartbeat while at rest during WEGOVY treatment. If patients experience a sustained increase in resting heart rate, discontinue WEGOVY.

Suicidal Behavior and Ideation: Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with WEGOVY for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue WEGOVY in patients who experience suicidal thoughts or behaviors. Avoid WEGOVY in patients with a history of suicidal attempts or active suicidal ideation.

Adverse Effects

Adverse Reaction %	Placebo n = 1261 %	Wegovy 2.4 mg n = 2116 %	Placebo n = 262 %	Ozempic 0.5 mg n = 260 %	Ozempic 1 mg n = 261 %
Nausea	16	44	6.1	15.8	20.3
Diarrhea	16	30	1.9	8.5	8.8
Vomiting	6	24	2.3	5.0	9.2
Constipation	11	24	1.5	5.0	3.1
Abdominal Pain	10	20	4.6	7.3	5.7

Injection site reactions: In placebo-controlled trials, injection site reactions were reported in 0.2% of OZEMPIC treated patients. 1.4% of WEGOVY treated patients and 1.0% of patients receiving placebo experienced injection site reactions.

Increases in amylase and lipase: In placebo-controlled trials, patients exposed to OZEMPIC had a mean increase from baseline in amylase of 13% and lipase of 22%. Patients treated with WEGOVY had a mean increase from baseline in amylase of 16% and lipase of 39%. These changes were not observed in the placebo group (with either OZEMPIC or WEGOVY). The clinical significance of elevations in lipase or amylase with semaglutide is unknown in the absence of other signs and symptoms of pancreatitis.

Monitoring

Monitor plasma glucose, HbA1c, renal function, signs/symptoms of pancreatitis, triglycerides, and signs/symptoms of gallbladder disease.

Interactions

- Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin: When initiating semaglutide, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.
- Oral Medications: Semaglutide causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, semaglutide did not affect the absorption of orally administered medications to any clinically relevant degree.

Nonetheless, caution should be exercised when oral medications are concomitantly administered with semaglutide.

Efficacy

OZEMPIC: To establish the cardiovascular safety of semaglutide (OZEMPIC), Marso and colleagues conducted a randomized, double-blind, placebo-controlled trial (SUSTAIN-6) at 230 sites in 20 countries.

3297 patients with type 2 diabetes (A1c > 7%) were randomized to receive either 0.5 mg or 1.0 mg of once-weekly OZEMPIC or volume-matched placebo along with guideline-based cardiovascular risk management (antihypertensives, lipid-lowering agents, anti-platelet medications). Eligible patients had been treated with no more than two oral antihyperglycemic agents, with or without basal or premixed insulin. Patients > 50 years old were required to have established cardiovascular disease, chronic heart failure (NYHA class II or III), or CKD of stage 3 or higher. Patients > 60 years old were required to have at least one cardiovascular risk factor.

Exclusion criteria included the following: treatment with a dipeptidyl-peptidase 4 inhibitor within 30 days before screening; treatment with a GLP-1 receptor agonist or insulin other than basal or premixed within 90 days before screening; history of an acute coronary or cerebrovascular event within 90 days before randomization; planned revascularization of a coronary, carotid, or peripheral artery; long-term dialysis.

Of the 3297 patients, 2735 (83.0%) had established cardiovascular disease (including CKD stage 3 or higher). Median observation time was 2.1 years. The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The composite primary outcome occurred in 108 of 1648 patients (6.6%) in the OZEMPIC group and 146 of 1649 (8.9%) in the placebo group (hazard ratio, 0.74; 95% CI 0.58 to 0.95, p <0.001 for noninferiority; p = 0.02 for superiority. Similar risk reductions for the primary outcome were seen for both doses of OZEMPIC.

At week 104, in patients receiving OZEMPIC, mean glycated hemoglobin level decreased from 8.7% at baseline to 7.6% in the 0.5 mg group and to 7.3% in the 1.0 mg group (changes of -1.1% and -1.4%). In the placebo group, the mean level decreased to 8.3% (change of – 0.4%). Compared with the placebo group, average body weight was 2.9 kg lower in patients taking OZEMPIC 0.5 mg and 4.3 kg lower in patients taking OZEMPIC 1.0 mg.

Diabetic retinopathy complications occurred in 50 patients (3.0%) in the OZEMPIC group versus 29 (1.8%) in the placebo group (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; p = 0.02). Of the patients who experienced retinopathy complications, 83.5% had retinopathy at baseline. Rates of new or worsening nephropathy were lower in the OZEMPIC group (3.8% in the semaglutide group versus 6.1% in the placebo

group, HR = 0.64; 95% CI, 0.46 to 0.88; p = 0.005). Approximately 13% of patients taking OZEMPIC stopped treatment because of adverse events (mainly gi) versus 6.7% of patients taking placebo.

WEGOVY:

In a double-blind, randomized, mult-center trial (STEP 1), Wilding and colleagues enrolled 1961 obese or overweight adults to 68 weeks of treatment with WEGOVY 2.4 mg SC once weekly (1306) or placebo (655); participants also received lifestyle intervention. Inclusion criteria included BMI > 30 or BMI > 27 plus at least one treated or untreated coexisting condition (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). Exclusion criteria included diabetes (HgA1c > 6.5%), a history of chronic pancreatitis, acute pancreatitis within 180 days before enrollment, previous surgical obesity treatment, and use of anti-obesity medication within 90 days before enrollment.

For the first four weeks, WEGOVY was started at a weekly dose of 0.25 mg SC. The dose was increased every four weeks until a maintenance dose of 2.4 mg weekly was reached at week 16. Lower maintenance doses were permitted if an individual could not tolerate the 2.4 mg weekly dose. Lifestyle interventions included monthly counseling sessions to help them adhere to a reduced calorie diet (500 kcal-deficit per day relative to their estimated energy expenditure at randomization) and increased physical activity (150 minutes per week encouraged). Participants made daily recordings of diet and activity in a diary or smart-phone app and these were reviewed during the counseling sessions.

The majority of participants were female (74.1%) and white (75.1%) and the average age was 46 yo. Mean baseline weight was 105.3 kg, BMI = 37.9. 44% had pre-diabetes and 75% had at least one coexisting condition.

In total, 91.2% of participants had a bodyweight assessment at week 68 and 81.1% adhered to treatment. In the WEGOVY group, weight loss was seen at the first assessment (week 4) and continued through week 60. Estimated mean weight change at week 68 was -14.9% with 2.4 mg WEGOVY and -2.4% with placebo (estimated difference = -12.4 percentage points, 95% CI = -13.4 to -11.5; p < 0.001). Compared to the placebo group, more individuals who took WEGOVY achieved weight reductions of 5% or more (86.4% vs 31.5%), 10% or more (69.1% vs 12.0%), and 15% or more (50.5% vs 4.9%) at week 68. Average weight loss (at 68 weeks) was -15.3 kg in the WEGOVY group versus -2.6 kg in the placebo group (estimated treatment difference = -12.7 kg; 95% CI, -13.7 to -11.7)

Compared to placebo, WEGOVY was associated with greater reductions from baseline in systolic and diastolic blood pressure, glycated hemoglobin, fasting plasma glucose, C-reactive protein and fasting lipids.

GI disorders (nausea, diarrhea, vomiting, constipation) were the most frequently reported adverse event. They occurred in 74.2% of patients taking WEGOVY versus 47.9% of those taking placebo. Most GI events were mild-moderate in severity and resolved without the need for treatment discontinuation. Serious gi disorders occurred in 1.4% of patients taking WEGOVY versus 0% of those taking placebo. Gallbladder-related disorders (mostly cholelithiasis) were reported in 2.6% of patients taking WEGOVY versus 1.2% of those taking placebo.

Dosage Forms/Cost (GoodRX)

OZEMPIC

$ 884.82 per single-patient-use pen

- 2 mg/1.5 ml, delivers 0.25 mg or 0.5 mg per injection
- 4 mg/3 ml, delivers 1 mg per injection
- 8 mg/3 ml, delivers 2 mg per injection

WEGOVY

$1333.91 per carton (4 pre-filled single dose pens)

- 0.25 mg/0.5 ml
- 0.5 mg/0.5 ml
- 1 mg/0.5 ml
- 1.7 mg/0.75 ml
- 2.4 mg/0.75 ml

Special Considerations

Morris-Dickson SH-SSLC purchases, 3/1/22-10/2/22

Medication	Pkg Size	Avg Cost	Item Qty	Item Total
Trulicity 0.75 mg	4 pens	$814.64	16	$13,034
Trulicity 1.5 mg	4 pens	$803.57	48	$38,571
Trulicity 3.0 mg	4 pens	$809.11	8	$6,473
Trulicity 4.5 mg	4 pens	$803.25	17	$13,655
Victoza	3 pens	$1064.61	28	$29,809
Victoza	2 pens	$709.74	14	$9936

Medication	Pkg Size	Avg Cost	Item Qty	Item Total
Ozempic 0.5 mg	1 multi-dose pen	$892.06	18	$16,057
Ozempic 1 mg	1 multi-dose pen	$892.06	17	$15,165
Rybelsus 14 mg	30	$892	7	$6244
Rybelsus 7 mg	30	$892	7	$6244
Rybelsus 3 mg	30	$892	3	$2676
Wegovy 0.5 mg	4	$1349	2	$2698
Wegovy 2.4 mg	4	$1349	2	$2698

Summary/Conclusion

Along with SGLT2i with proven CVD benefit, ADA 2022 recommends GLP-1 receptor agonists with proven CVD benefit (with or without metformin) as appropriate initial therapy for individuals with type 2 diabetes with or at high risk for ASCVD. These agents include liraglutide (Victoza), dulaglutide (Trulicity), and subcutaneous semaglutide (Ozempic, Wegovy). GLP-1 receptor agonists are also a first line choice for CV risk reduction in diabetics patients with CKD without albuminuria. If injectable therapy is needed to reduce A1c, ADA 2022 also recommends GLP-1 RA over insulin, when possible.

In 2019, liraglutide (Victoza) was added to the formulary because, at the time, it was the most widely used glp-1 receptor agonist in the state system and the only glp-1 approved to reduce CV risk in patients with established CV disease. It had also shown efficacy in the treatment of metabolic disturbances in patients treated with antipsychotics. In July 2022, dulaglutide (Trulicity) was added to the formulary. Dulaglutide is approved to reduce MACE in adults with type 2 diabetes who have established cardiovascular disease or multiple cardiovascular risk factors.

Compared to the short-acting GLP-1 RA's (exenatide IR [Byetta], lixisenatide [Adlyxin]), long acting GLP-1RA's are better at glucose-lowering and weight reduction and semaglutide is considered the most effective agent in the class. In the SUSTAIN-7 study, semaglutide (Ozempic) showed superiority over dulaglutide (Trulicity) in improving glycemic control and weight loss>5%. Compared to liraglutide's (Saxenda) placebo-controlled weight management trial (SCALE),

semaglutide's (Wegovy) placebo-controlled trials (STEP program) showed greater mean weight loss and a greater percentage of patients who lost at least 5% of their body weight.

Recommendation

OZEMPIC and WEGOVY should be added to the formulary.

References

1. Singh G, Krauthamer M, Bjalme-Evans M. Wegovy (semaglutide): a new weight loss drug for chronic weight management. *J Investig Med* 2022: 70: 5-13.
2. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. SUSTAIN-6. N Engl J Med 2016; 375: 1834-44.
3. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomized, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018; 6: 275-86.
4. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. STEP 1. *N Engl J Med* 2021;384: 989-1002.
5. Wegovy-semaglutide injection solution, prescribing information. Novo Nordisk. Revised 6/2021.
6. Ozempic-semaglutide injection solution, prescribing information. Novo Nordisk. Revised 3/2022.
7. Latif W, Lambrinos KJ, Rodriguez R. Compare and contrast the glucagon-like peptide-1 receptor agonists (GLP1RAs) [Updated 2021 Jul 5]. In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing: 2022 Jan
8. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2022;45(Suppl. 1):S125-S143

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Appendix D

semaglutide (Rybelsus®)

Classification

Antidiabetic agent

Pharmacology

Semaglutide is a human glucagon-like peptide 1 (GLP-1) receptor agonist (incretin mimetic). Semaglutide activates the GLP-1 receptor in pancreatic beta cells leading to glucose-dependent insulin release. It also decreases glucagon secretion, slows gastric emptying, and promotes satiety. Oral semaglutide is co-formulated with the absorption enhancer salcaprozate sodium.

Indication

RYBELSUS is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use:

- Not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans.
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not indicated for use in patients with type 1 diabetes mellitus.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Occurs in stomach. Co-formulated with salcaprozate sodium to facilitate absorption. Bioavailability = 0.4%-1%
Distribution	>99% bound to albumin
Metabolism	Proteolytic cleavage of peptide backbone, beta-oxidation of fatty acid side chain; half life = 1 week
Excretion	Urine, feces. 3% of absorbed dose excreted in urine as intact semaglutide.

Dosage/Administration

Take RYBELSUS at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only. Waiting less than 30 minutes, or taking RYBELSUS with food, beverages (other than plain water)

or other oral medications will lessen the effect of RYBELSUS by decreasing its absorption. Waiting more than 30 minutes to eat may increase the absorption of RYBELSUS.

Swallow tablets whole. Do not split, crush, or chew tablets.

Start with 3 mg once daily for 30 days. The 3 mg dose is intended for treatment initiation and is not effective for glycemic control. After 30 days on the 3 mg dose, increase the dose to 7 mg once daily. Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose. If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

Switching Patients between Ozempic and Rybelsus:

Patients treated with Rybelsus 14 mg daily can be transitioned to Ozempic subcutaneous injection 0.5 mg once weekly. Patients can start Ozempic the day after their last dose of Rybelsus.

Patients treated with once weekly Ozempic 0.5 mg subcutaneous injection can be transitioned to Rybelsus 7 mg or 14 mg. Patients can start Rybelsus up to 7 days after their last injection of Ozempic. There is no equivalent dose of Rybelsus for Ozempic 1 mg.

Use in Special Population

Pregnancy: Available data with RYBELSUS use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to RYBELSUS during pregnancy. RYBELSUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at exposure below the MRHD (rabbit) and ≥10-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species.

Lactation: There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats. Salcaprozate sodium (SNAC), an absorption enhancer in Rybelsus, crosses the placenta and reaches fetal tissues in rats. SNAC and/or its metabolites concentrated in the milk of lactating rats. When a substance is

present in animal milk, it is likely that the substance will be present in human milk (see Data). There are no data on the presence of SNAC in human milk. Since the activity of UGT2B7, an enzyme involved in SNAC clearance, is lower in infants compared to adults, higher SNAC plasma levels may occur in neonates and infants. Because of the unknown potential for serious adverse reactions in the breastfed infant due to the possible accumulation of SNAC from breastfeeding and because there are alternative formulations of semaglutide that can be used during lactation, advise patients that breastfeeding is not recommended during treatment with RYBELSUS.

Females and Males of Reproductive Potential: Discontinue RYBELSUS in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

Pediatric Use: Safety and efficacy of Rybelsus have not been established in pediatric patients (younger than 18 years).

Geriatric Use: In the pool of glycemic control trials, 1229 (29.9%) RYBELSUS-treated patients were 65 years of age and over and 199 (4.8%) RYBELSUS-treated patients were 75 years of age and over. In PIONEER 6, the cardiovascular outcomes trial, 891 (56.0%) RYBELSUS-treated patients were 65 years of age and over and 200 (12.6%) RYBELSUS-treated patients were 75 years of age and over.

No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment: The safety and efficacy of RYBELSUS was evaluated in a 26-week clinical study that included 324 patients with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m). In patients with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed.

No dose adjustment of RYBELSUS is recommended for patients with renal impairment.

Hepatic Impairment: In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed. No dose adjustment of RYBELSUS is recommended for patients with hepatic impairment.

Contraindication

Personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia Syndrome Type 2 (MEN 2).

Prior hypersensitivity reaction to semaglutide or to any of the excipients in Rybelsus. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with Rybelsus.

Precautions

Risk of Thyroid C-Cell Tumors: In mice and rats, semaglutide caused a dose-dependent and treatment-duration dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether RYBELSUS causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

RYBELSUS is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of RYBELSUS and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with RYBELSUS. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Pancreatitis: In glycemic control trials, pancreatitis was reported as a serious adverse event in 6 RYBELSUS-treated patients (0.1 events per 100 patient years) versus 1 in comparator-treated patients (<0.1 events per 100 patient years).

After initiation of RYBELSUS, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, RYBELSUS should be discontinued and appropriate management initiated; if confirmed, RYBELSUS should not be restarted.

Diabetic Retinopathy Complications: In a pooled analysis of glycemic control trials with RYBELSUS, patients reported diabetic retinopathy related adverse reactions during the trial (4.2% with RYBELSUS and 3.8% with comparator).

In a 2-year cardiovascular outcomes trial with semaglutide injection involving patients with type 2 diabetes and high cardiovascular risk, diabetic retinopathy complications (which was a 4 component adjudicated endpoint) occurred in patients treated with semaglutide injection (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (semaglutide injection 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide injection 0.7%, placebo 0.4%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: Patients receiving RYBELSUS in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Acute Kidney Injury: There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists, including semaglutide. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of RYBELSUS in patients reporting severe adverse gastrointestinal reactions.

Hypersensitivity: Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with RYBELSUS. If hypersensitivity reactions occur, discontinue use of RYBELSUS; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to RYBELSUS.

Anaphylaxis and angioedema have been reported with GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with RYBELSUS.

Acute Gallbladder Disease: Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In placebo-controlled trials, cholelithiasis was reported in 1% of patients treated with RYBELSUS 7 mg. Cholelithiasis was not reported in RYBELSUS 14 mg or placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Adverse Effects

Adverse effect	Placebo (n = 362) %	Rybelsus 7 mg (n = 356) %	Rybelsus 14 mg (n = 356) %
Nausea	6	11	20
Abdominal pain	4	10	11
Diarrhea	4	9	10
Decreased appetite	1	6	9
Vomiting	3	6	8
Constipation	2	6	5

Increases in Amylase and Lipase: Patients exposed to Rybelsus 7 mg and 14 mg had mean increase from baseline in amylase of 10% and 13%, respectively, and lipase of 30% and 34%, respectively. These changes were not observed in placebo-treated patients.

Monitoring

Plasma glucose, HbA1c, heart rate and body weight, renal function (especially when initiating therapy or increasing doses in patients reporting severe adverse GI reactions); signs/symptoms of pancreatitis, triglycerides; signs/symptoms of gallbladder disease; worsening of diabetic retinopathy (particularly in those with a prior history of the disease).

Interactions

Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin: When initiating RYBELSUS, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.

Oral Medications: RYBELSUS causes a delay of gastric emptying, and thereby has the potential to impact the absorption of other oral medications. Levothyroxine exposure was increased 33% when administered with RYBELSUS in a drug interaction study.

When coadministering oral medications instruct patients to closely follow RYBELSUS administration instructions. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or that require clinical monitoring.

Efficacy

PIONEER 6: In a randomized, double-blind, placebo-controlled trial, Husain and colleagues assessed cardiovascular outcomes of once-daily oral semaglutide. The study's purpose was to rule out an excess in cardiovascular risk with oral semaglutide in patients with type 2 diabetes.

Patients were at high cardiovascular risk. Inclusion criteria included age > 50 years with established cardiovascular disease or chronic kidney disease or age > 60 with cardiovascular risk factors. Exclusion criteria included treatment with any GLP-1 receptor agonist, dipeptidyl peptidase 4 inhibitor, or pramlintide within 90 days before screening; NYHA class 4 heart failure; planned coronary-artery, carotid-artery, or peripheral-artery revascularization; myocardial infarction, stroke, or hospitalization for unstable angina or TIA within 60 days before screening; long-term or intermittent hemodialysis or peritoneal dialysis, or severe renal impairment (estimated GFR < 30 ml per minute); proliferative retinopathy or maculopathy resulting in active treatment.

3183 patients were randomized to receive once daily semaglutide (n = 1591) or placebo (n = 1592) in addition to standard of care treatment. The target dose of semaglutide was 14 mg. Investigators maintained and intensified patients' glucose-lowering and cardiovascular medication in accordance with local and international guidelines. A dose escalation schedule was used to decrease gi side effects. Median time in the trial was 15.9 months; 75% of the patients received oral semaglutide or placebo for more than one year.

Sixty-eight (68.4%) of patients were male and 84.7% were >50 and had established cardiovascular disease or chronic kidney disease. At baseline, mean (+ SD) body weight was 90.9 + 21.2 kg, mean HgA1c = 8.2 + 1.6%, mean age 66 + 7 years, mean duration of diabetes 14.9 + 8.5 years.

The primary outcome was time to first occurrence of a major adverse cardiovascular event (composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The primary outcome occurred in 61 of 1591 patients (3.8%) receiving oral semaglutide and 76 of 1592 (4.8%) receiving placebo (21% difference in risk, HR = 0.79, 95% CI = 0.57 to 1.11, p < 0.001 for noninferiority, p = 0.17 for

superiority). Mean change from baseline to end point for HgA1c and body weight were -1.0% (oral semaglutide) versus -0.3% (placebo and -4.2 kg versus -0.8 kg.

Serious adverse events occurred in 301/1591 (18.9%) patients in the oral semaglutide group and 358/1592 (22.5%) patients in the placebo group. These were varied and attributed to several different organ systems. More patients stopped taking oral semaglutide than placebo (11.6% versus 6.5%), mainly because more gi adverse events occurred in the semaglutide versus the placebo group (6.8% versus 1.6%).

Dosage Forms/Cost

Tablets: 3 mg, 7 mg, 14 mg. $884.81 per month. GoodRx.

Special Considerations

Medication	Pkg Size	Avg Cost	Item Qty	Item Total
Ozempic 0.5mg, 1mg	1 multi-dose pen	$892.06	35	$31,222
Rybelsus 14mg, 7mg, 3mg	30	$892	17	$15,164
Wegoxy 0.5mg, 2.4mg	4	$1349	4	$5,396

Summary/Conclusion

In 2019, the FDA approved semaglutide (Rybelsus), the first oral glucagon-like peptide I receptor agonist (GLP-I) as an adjunct to diet and exercise for the treatment of type 2 diabetes. The absorption enhancer salcaprozate sodium aids semaglutide's absorption through the gastic mucosa, preventing its rapid degradation in the stomach. For Rybelsus to be fully efficacious, it must be taken daily at least 30 minutes before the first food, other beverage, or oral meds of the day with no more than four ounces of water.

In the PIONEER 1 trial, monotherapy with semaglutide 7 mg and 14 mg once daily for 26 weeks resulted in statistically significant reductions in A1c compared with placebo (-1.2% [95% CI -1.5%, -1%] and –1.4% [95% CI -1.7%, -1.2%], respectively). Semaglutide (Rybelsus) 14 mg also significantly reduced body weight compared to placebo (-2.6 kg [95% CI: -3.4 to -1.8 kg]). In the PIONEER 6 cardiovascular outcomes trial (CVOT), oral semaglutide was non-inferior to placebo with respect to cardiovascular safety; further cardiovascular outcomes trials are in process.

Recommendation

Oral semaglutide (Rybelsus) should be added to the formulary.

References

1. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1 Investigators. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. *Diabetes Care.* 2019;42:1724-1732.
2. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. PIONEER 6. N Engl J Med 2019;381: 841-51.
3. RYBELSUS—oral semaglutide tablet Prescribing Information. Novo Nordisk. Revised 6/2022.
4. Cowart K. Oral Semaglutide: First-in-Class Oral GLP-1 Receptor Agonist for the Treatment of Type 2 Diabetes Mellitus. Annals of Pharmacotherapy 2020. Vol 54(5) 478-485.
5. Latif W, Lambrinos KJ, Rodriguez R. Compare and contrast the glucagon-like peptide-1 receptor agonists (GLP1RAs) [Updated 2021 Jul 5]. In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing: 2022 Jan
6. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2022;45(Suppl. 1):S125-S143

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Appendix E

Clonidine Hydrochloride ER (Kapvay®)

Classification

Alpha-2 adrenergic agonist, centrally acting

Pharmacology

Clonidine stimulates alpha2-adrenergic receptors in the brain. Clonidine is not a central nervous system stimulant. The mechanism of action of clonidine in ADHD is not known.

Black Box Warning

None.

Indication

KAPVAY™ (clonidine hydrochloride) extended-release is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications.

NOTE: This extended-release formulation of clonidine hydrochloride is also approved for the treatment of hypertension in adults under the trade name JENLOGA.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Tmax = 6.5 h; Bioavailability 89% of the immediate-release, extended release. Food had minimal effect on plasma concentrations, absorption, or elimination.
Distribution	Vd: 2.1 L/kg, Vd (children): 0.96 L/kg; Protein binding 20% to 40%
Metabolism	Hepatic: 50%
Excretion	Fecal: 22%; Renal: 40% to 60% unchanged; Half-life (adults): 12.5 to 16 h; Half-life (pediatric): 5.6 h; Half-life 9renal impairment): up to 41 h

Dosage/Administration

KAPVAY is an extended-release tablet formulation of clonidine hydrochloride. While it is dosed twice a day, the same as the immediate-release clonidine formulation, it is not to be used interchangeably with the immediate-release formulation.

KAPVAY is an extended-release tablet and, therefore, must be swallowed whole and never crushed, cut or chewed. KAPVAY may be taken with or without food.

Due to the lack of controlled clinical trial data and differing pharmacokinetic profiles, substitution of KAPVAY for other clonidine products on a mg-per-mg basis is not recommended.

The dose of KAPVAY, administered either as monotherapy or as adjunctive therapy to a psychostimulant, should be individualized according to the therapeutic needs and response of the patient. Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved. Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime (see Table 1).

Table 1 KAPVAY Dosing Guidance

Total Daily Dose	Morning Dose	Bedtime Dose
0.1 mg/day	na	0.1 mg
0.2 mg/day	0.1 mg	0.1 mg
0.3 mg/day	0.1 mg	0.2 mg
0.4 mg/day	0.2 mg	0.2 mg

Doses of KAPVAY higher than 0.4 mg/day (0.2 mg twice daily) were not evaluated in clinical trials for ADHD and are not recommended.

When KAPVAY is being added-on to a psychostimulant, the dose of the psychostimulant can be adjusted depending on the patient's response to KAPVAY.

Maintenance Treatment: The effectiveness of KAPVAY for longer-term use (more than 5 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician electing to use KAPVAY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Discontinuation: When discontinuing KAPVAY, the total daily dose should be tapered in decrements of no more than 0.1 mg every 3 to 7 days.

Use in Special Population

Pregnancy: Prolonged experience with clonidine in pregnant women over several decades, based on published literature, including controlled trials, a retrospective cohort study and case reports, have not identified a drug associated risk of major

birth defects, miscarriage, and adverse maternal or fetal outcomes. In animal embryofetal studies, increased resorptions were seen in rats and mice administered oral clonidine hydrochloride from implantation through organogenesis at 10 and 5 times, respectively, the maximum recommended human dose (MRHD) given to adolescents on a mg/m2 basis. No developmental effects were seen in rabbits administered oral clonidine hydrochloride during organogenesis at doses up to 3 times the MRHD.

Lactation: Based on published lactation studies, clonidine hydrochloride is present in human milk at relative infant doses ranging from 4.1 to 8.4% of the maternal weight-adjusted dosage. Although in most cases, there were no reported adverse effects in breastfed infants exposed to clonidine, there is one case report of sedation, hypotonia, and apnea in an infant exposed to clonidine through breast milk. If an infant is exposed to clonidine hydrochloride through breastmilk, monitor for symptoms of hypotension and bradycardia, such as sedation, lethargy, tachypnea and poor feeding (see Clinical Considerations). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KAPVAY and any potential adverse effects on the breastfed child from KAPVAY or from the underlying maternal condition. Exercise caution when KAPVAY is administered to a nursing woman.

Clinical Considerations: Monitor breastfeeding infants exposed to KAPVAY through breast milk for symptoms of hypotension and/or bradycardia such as sedation, lethargy, tachypnea, and poor feeding.

Females and Males of Reproductive Potential (Infertility): Based on findings in Animal studies revealed that KAPVAY may impair fertility in females and males of reproductive potential.

Pediatric Use: The safety and efficacy of KAPVAY in the treatment of ADHD have been established in pediatric patients 6 to 17 years of age. Use of KAPVAY in pediatric patients 6 to 17 years of age is supported by three adequate and well-controlled studies; a short-term, placebo-controlled monotherapy trial, a short-term adjunctive therapy trial and a longer-term randomized monotherapy trial. Safety and efficacy in pediatric patients below the age of 6 years has not been established.

Renal Impairment: The impact of renal impairment on the pharmacokinetics of clonidine in children has not been assessed. The initial dosage of KAPVAY should be based on degree of impairment. Monitor patients carefully for hypotension and bradycardia and titrate to higher doses cautiously. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental KAPVAY following dialysis

Contraindication

KAPVAY is contraindicated in patients with a history of a hypersensitivity reaction to clonidine. Reactions have included generalized rash, urticaria, and angioedema.

Precautions

Hypotension/Bradycardia: Hypotension/Bradycardia Treatment with KAPVAY can cause dose-related decreases in blood pressure and heart rate. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Titrate KAPVAY slowly in patients with a history of hypotension, and those with underlying conditions that may be worsened by hypotension and bradycardia, e.g., heart block, bradycardia, cardiovascular disease, vascular disease, cerebrovascular disease, or chronic renal failure. In patients who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration, advise patients to avoid becoming dehydrated or overheated. Monitor blood pressure and heart rate and adjust dosages accordingly in patients treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope.

Sedation and Somnolence: Somnolence and sedation were commonly reported adverse reactions in clinical studies. In patients that completed 5 weeks of therapy in a controlled, fixed dose pediatric monotherapy study, 31% of patients treated with 0.4 mg/day and 38% treated with 0.2 mg/day versus 4% of placebo treated patients reported somnolence as an adverse event. In patients that completed 5 weeks of therapy in a controlled flexible dose pediatric adjunctive to stimulants study, 19% of patients treated with KAPVAY+ stimulant versus 7% treated with placebo+ stimulant reported somnolence. Before using KAPVAY with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), consider the potential for additive sedative effects. Caution patients against operating heavy equipment or driving until they know how they respond to treatment with KAPVAY. Advise patients to avoid use with alcohol.

Rebound Hypertension: Abrupt discontinuation of KAPVAY can cause rebound hypertension. In adults with hypertension, sudden cessation of clonidine hydrochloride extended-release formulation treatment in the 0.2 to 0.6 mg/day range resulted in reports of headache, tachycardia, nausea, flushing, warm feeling, brief lightheadedness, tightness in chest, and anxiety. In adults with hypertension, sudden cessation of treatment with immediate-release clonidine has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. No studies evaluating abrupt discontinuation of KAPVAY in children with ADHD have been conducted; however, to minimize the risk of rebound hypertension, gradually reduce the dose of KAPVAY in decrements of no more than 0.1 mg every 3 to 7 days. Patients should be instructed

not to discontinue KAPVAY therapy without consulting their physician due to the potential risk of withdrawal effects.

Allergic Reactions: In patients who have developed localized contact sensitization to clonidine transdermal system, continuation of clonidine transdermal system or substitution of oral KAPVAY therapy may be associated with the development of a generalized skin rash. In patients who develop an allergic reaction from clonidine transdermal system, substitution of oral KAPVAY may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

Cardiac Conduction Abnormalities: The sympatholytic action of clonidine may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. There have been post-marketing reports of patients with conduction abnormalities and/or taking other sympatholytic drugs who developed severe bradycardia requiring IV atropine, IV isoproterenol, and temporary cardiac pacing while taking clonidine. Titrate KAPVAY slowly and monitor vital signs frequently in patients with cardiac conduction abnormalities or patients concomitantly treated with other sympatholytic drugs.

Adverse Effects

Most common adverse reactions (incidence at least 5% and twice the rate of placebo) as monotherapy in ADHD: somnolence (31% to 38%), fatigue (13% to 16%), irritability (5% to 9%), nightmare (4% to 9%), insomnia (5% to 6%), constipation (1% to 6%), and dry mouth (5%).

Most common adverse reactions (incidence at least 5% and twice the rate of placebo) as adjunct therapy to psychostimulant in ADHD: somnolence (19%), fatigue (14%), decreased appetite (6%), and dizziness (5%).

Common Adverse Reactions in the Fixed-Dose Monotherapy Trial - Treatment Period (Study 1)

	Percentage of Patients Reporting Event		
Preferred Term	**KAPVAY 0.2 mg/day N=76**	**KAPVAY 0.4 mg/day N=78**	**Placebo (N=76)**
PSYCHIATRIC DISORDERS			
Somnolence*	38%	31%	4%
Nightmare	4%	9%	0%
Emotional Disorder	4%	4%	1%
Aggression	3%	1%	0%
Tearfulness	1%	3%	0%
Enuresis	0%	4%	0%
Sleep Terror	3%	0%	0%
Poor Quality Sleep	0%	3%	1%
NERVOUS SYSTEM DISORDERS			
Headache	20%	13%	16%
Insomnia	5%	6%	1%
Tremor	1%	4%	0%
Abnormal Sleep-Related Event	3%	1%	0%
GASTROINTESTINAL DISORDERS			
Upper Abdominal Pain	15%	10%	12%
Nausea	4%	5%	3%
Constipation	1%	6%	0%
Dry Mouth	0%	5%	1%
GENERAL DISORDERS			
Fatigue†	16%	13%	1%
Irritability	9%	5%	4%
CARDIAC DISORDERS			
Dizziness	7%	3%	5%
Bradycardia	0%	4%	0%
INVESTIGATIONS			
Increased Heart Rate	0%	3%	0%
METABOLISM AND NUTRITION DISORDERS			
Decreased Appetite	3%	4%	4%

* Somnolence includes the terms "somnolence" and "sedation".

† Fatigue includes the terms "fatigue" and "lethargy".

Common Adverse Reactions in the Flexible-Dose Adjunctive to Stimulant Therapy Trial - Treatment Period (Study 2)

Preferred Term	Percentage of Patients Reporting Event	
	KAPVAY+STM (N=102)	PBO+STM (N=96)
PSYCHIATRIC DISORDERS		
Somnolence*	19%	7%
Aggression	2%	1%
Affect Lability	2%	1%
Emotional Disorder	2%	0%
GENERAL DISORDERS		
Fatigue†	14%	4%
Irritability	2%	7%
NERVOUS SYSTEM DISORDERS		
Headache	7%	12%
Insomnia	4%	3%
GASTROINTESTINAL DISORDERS		
Upper Abdominal Pain	7%	4%
RESPIRATORY DISORDERS		
Nasal Congestion	2%	2%
METABOLISM AND NUTRITION DISORDERS		
Decreased Appetite	6%	3%
CARDIAC DISORDERS		
Dizziness	5%	1%

* Somnolence includes the terms "somnolence" and "sedation".
† Fatigue includes the terms "fatigue" and "lethargy".

Effect on Blood Pressure and Heart Rate: In patients that completed 5 weeks of treatment in a controlled, fixed-dose monotherapy study in pediatric patients, during the treatment period the maximum placebo-subtracted mean change in systolic blood pressure was -4.0 mmHg on KAPVAY 0.2 mg/day and -8.8 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in diastolic blood pressure was -4.0 mmHg on KAPVAY 0.2 mg/day and -7.3 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in heart rate was -4.0 beats per minute on KAPVAY 0.2 mg/day and -7.7 beats per minute on KAPVAY 0.4 mg/day.

During the taper period of the fixed-dose monotherapy study the maximum placebo-subtracted mean change in systolic blood pressure was +3.4 mmHg on KAPVAY 0.2 mg/day and -5.6 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in diastolic blood pressure was +3.3 mmHg on KAPVAY 0.2 mg/day and -5.4 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in heart rate was -0.6 beats per minute on KAPVAY 0.2 mg/day and -3.0 beats per minute on KAPVAY 0.4 mg/day.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of KAPVAY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Psychiatric: hallucinations

Cardiovascular: Q-T prolongation

Monitoring

Titrate slowly and monitor vital signs frequently in patients at risk for hypotension, heart block, bradycardia, syncope, cardiovascular disease, vascular disease, cerebrovascular disease, or chronic renal failure.

Interactions

Clinically Important Drug Interactions

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Tricyclic antidepressants	Increase blood pressure and may counteract clonidine's hypotensive effects	Monitor blood pressure and adjust as needed
Antihypertensive drugs	Potentiate clonidine's hypotensive effects	Monitor blood pressure and adjust as needed
CNS depressants	Potentiate sedating effects	Avoid use
Drugs that affect sinus node function or AV node conduction (e.g., digitalis, calcium channel blockers, beta blockers)	Potentiate bradycardia and risk of AV block	Avoid use

Efficacy

Efficacy of KAPVAY in the treatment of ADHD was established in children and adolescents (6 to 17 years) in:

- One short-term, placebo-controlled monotherapy trial (Study 1 CLON-301)
- One short-term adjunctive therapy to psychostimulants trial (Study 2 CLON-302)
- One randomized withdrawal trial as monotherapy (Study 3 SHN-KAP-401)

Short-term Monotherapy and Adjunctive Therapy to Psychostimulant Studies for ADHD: The efficacy of KAPVAY in the treatment of ADHD was established in 2 (one monotherapy and one adjunctive therapy) placebo-controlled trials in pediatric

patients aged 6 to 17, who met DSM-IV criteria of ADHD hyperactive or combined hyperactive/inattentive subtypes. Signs and symptoms of ADHD were evaluated using the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS-IV) total score including hyperactive/impulsivity and inattentive subscales.

Study 1 (CLON-301), was an 8-week randomized, double-blind, placebo-controlled, fixed dose study of children and adolescents aged 6 to 17 (N=236) with a 5-week primary efficacy endpoint. Patients were randomly assigned to one of the following three treatment groups: KAPVAY (CLON) 0.2 mg/day (N=78), KAPVAY 0.4 mg/day (N=80), or placebo (N=78). Dosing for the KAPVAY groups started at 0.1 mg/day and was titrated in increments of 0.1 mg/week to their respective dose (as divided doses). Patients were maintained at their dose for a minimum of 2 weeks before being gradually tapered down to 0.1 mg/day at the last week of treatment. At both doses, improvements in ADHD symptoms were statistically significantly superior in KAPVAY-treated patients compared with placebo-treated patients at the end of 5 weeks as measured by the ADHDRS-IV total score (Table 8).

Study 2 (CLON-302), was an 8-week randomized, double-blind, placebo-controlled, flexible dose study in children and adolescents aged 6 to 17 (N=198) with a 5-week primary efficacy end point. Patients had been treated with a psychostimulant (methylphenidate or amphetamine) for four weeks with inadequate response. Patients were randomly assigned to one of two treatment groups: KAPVAY adjunct to a psychostimulant (N=102) or psychostimulant alone (N=96). The KAPVAY dose was initiated at 0.1 mg/day and doses were titrated in increments of 0.1 mg/week up to 0.4 mg/day, as divided doses, over a 3-week period based on tolerability and clinical response. The dose was maintained for a minimum of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. ADHD symptoms were statistically significantly improved in KAPVAY plus stimulant group compared with the stimulant alone group at the end of 5 weeks as measured by the ADHDRS-IV total score (Table 8).

Table 8 Short-Term Trials

Study Number	Treatment Group	Primary Efficacy Measure: ADHDRS-IV Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	KAPVAY (0.2 mg/day)	43.8 (7.47)	-15.0 (1.38)	-8.5 (-12.2, - 4.8)
	KAPVAY (0.4 mg/day)	44.6 (7.73)	-15.6 (1.33)	-9.1 (-12.8, - 5.5)
	Placebo	45.0 (8.53)	-6.5 (1.35)	--
Study 2	KAPVAY (0.4 mg/day) + Psychostimulant	38.9 (6.95)	-15.8 (1.18)	-4.5 (-7.8, -1.1)
	Psychostimulant alone	39.0 (7.68)	-11.3 (1.24)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.

Maintenance Monotherapy for ADHD: Study 3 (SHN-KAP-401), was a double-blind, placebo-controlled, randomized-withdrawal study in children and adolescents aged 6 to 17 years (n=253) with DSM-IV-TR diagnosis of ADHD. The study consisted

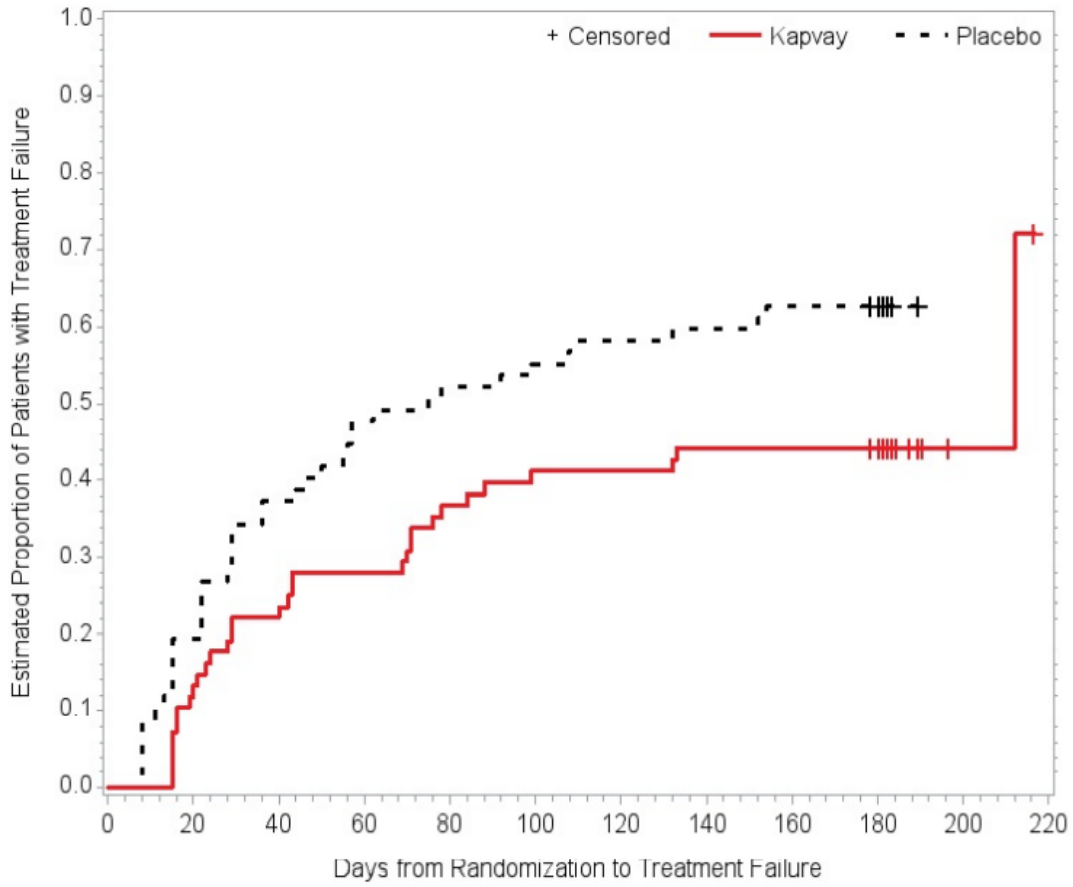
of a 10-week, open-label phase (4 weeks of dose optimization and 6 weeks of dose maintenance), a 26-week double-blind phase, and a 4-week taper-down and follow-up phase. All patients were initiated at 0.1 mg/day and increased at weekly intervals in increments of 0.1 mg/day until reaching personalized optimal dose (0.1, 0.2, 0.3 or 0.4 mg/day, as divided doses). Eligible patients had to demonstrate treatment response as defined by ≥ 30% reduction in ADHD-RS-IV total score and a Clinical Global Impression-Improvement score of 1 or 2 during the open label phase. Patients who sustained treatment response (n=135) until the end of the open label phase were randomly assigned to one of the two treatment groups, KAPVAY (N=68) and Placebo (N=67), to evaluate the long-term efficacy of maintenance dose of KAPVAY in the double-blind phase. The primary efficacy endpoint was the percentage of patients with treatment failure defined as a ≥ 30% increase (worsening) in ADHD-RS-IV total score and ≥ 2 points increase (worsening) in Clinical Global Impression – Severity Scale in 2 consecutive visits or early termination for any reason. A total of 73 patients experienced treatment failure in the double-blind phase: 31 patients (45.6%) in the KAPVAY group and 42 patients (62.7%) in the placebo group, with a statistically significant difference in the primary endpoint favoring KAPVAY (Table 9). The cumulative proportion of patients with treatment failure over time during the double-blind phase is displayed in Figure 2.

Table 9 Treatment Failure: Double-Blind Full Analysis Set (Study 3)

Study 3	Double-Blind Full Analysis Set	
	Kapvay®	Placebo
Number of subjects	68	67
Number of treatment failures	31 (45.6%)	42 (62.7%)
Basis of Treatment Failure		
Clinical criteria[a,b]	11 (16.2%)	9 (13.4%)
Lack of efficacy[c]	1 (1.5%)	3 (4.5%)
Withdrawal of informed assent/consent	4 (5.9%)	20 (29.9%)
Other early terminations	15 (22.1%)	10 (14.9%)

ADHD-RS-IV = Attention Deficit Hyperactivity Disorder-Rating Scale-4th edition; CGI-S = Clinical Global Impression-Severity
[a]At the same 2 consecutive visits a (1) 30% or greater reduction in ADHD-RS-IV, and (2) 2-point or more increase in CGI-S.
[b]Two subjects (1 placebo and 1 KAPVAY) withdrew consent, but met the clinical criteria for treatment failure.
[c] Three subjects (all placebo) discontinued the study due to treatment failure, but met only the criterion for ADHD-RS-IV.

Figure 2: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Treatment Failure (Study 3)



Dosage Forms/Cost

Available as 0.1 mg strength extended-release tablet. Tablets are round, white, non-scored, standard convex with debossing on one side.

Per Morris & Dickson, a 60-count bottle of 0.1 mg tablets is $500.00. Per GoodRx, month supply of each strength is $256.75

Recommendation

Clonidine extended release (Kapvay) should be added to the formulary.

References

1. Kapvay® (clonidine hydrocloride) extended-release tablets package insert. Revised: 02/2020.
2. Jain R, Segal S, Kollins SH, Khayrallah M. Clonidine extended-release tablets for pediatric patients with attention deficit/hyperactivity disorder (CLON-301). *J Am Acad Child Adoles Psychiatry* 2011; 50(2): 171-9.
3. Kollins SH, Jain R, Brams M, et al. Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD (CLON-302). *Pediatrics* 2011; 127(6): e1406-13.

4. Concordia Pharmaceuticals Inc., Barbados. Efficacy & Safety of Kapvay™ Extended-Release in Children & Adolescents With Attention Deficit Hyperactivity Disorder (Clinicaltrials.gov Identifier NCT01439126). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01439126
5. Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ Accessed [05/05/22].

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