CYCLOSET®
bromocriptine mesylate tablets

As an adjunct to diet and exercise for adult patients with type 2 diabetes mellitus (T2DM)[1]:

THINK CYCLOSET® FOR ADDED GLYCEMIC CONTROL[1]

The insulin sensitizer that uniquely targets dopamine D2 receptors[1]

YOUR GUIDE FOR IDENTIFYING AND PRESCRIBING APPROPRIATE PATIENTS

INDICATION

CYCLOSET® (bromocriptine mesylate) 0.8 mg tablets is a dopamine receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

LIMITATIONS OF USE

- CYCLOSET should not be used to treat type 1 diabetes or diabetic ketoacidosis.
- Limited efficacy data in combination with thiazolidinediones.
- Efficacy has not been confirmed in combination with insulin.

IMPORTANT SAFETY INFORMATION

Contraindications

CYCLOSET is contraindicated in:

- Patients with hypersensitivity to ergot-related drugs, bromocriptine or to any of the excipients in CYCLOSET.
- Patients with syncopal migraines. May precipitate hypotension.
- Postpartum patients. Serious and life-threatening adverse reactions have been reported.
- Lactating patients. CYCLOSET contains bromocriptine which inhibits lactation.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

WHEN SHOULD I CONSIDER CYCLOSET®?

Think of CYCLOSET® early as add-on therapy to help your patients with T2DM achieve their treatment goals

Consider treatment for patients in one or more of the following scenarios[1-5]:

- **Are just beyond their current HbA1c goals**[1]
  CYCLOSET® helped reduce HbA1c relative to placebo in a 24-week study[1,6,7,*,†,‡]
- **Have adequate insulin production and an existing antidiabetic regimen**[1]
  CYCLOSET® offers a targeted mechanism of action as a complementary add-on therapy[1]
- **Have elevated postprandial glucose despite adequate insulin production**[1,6]
  In a pharmacodynamic study, CYCLOSET® reduced plasma glucose at 1 and 2 hours after each meal[1,6,§,‖]
- **Have a history of hypertension with high triglycerides**[3,4,8,¶]
  Although CYCLOSET® is not indicated to reduce blood pressure[#] or plasma lipids,[†] patients saw reductions in clinical trials[1,6-8]
  - -2.0 mm Hg systolic vs 0.0 mm Hg and -2.0 mm Hg diastolic vs -1.0 mm Hg[8]
  - -29% triglycerides[6,7,**,††] and -19% free fatty acids across the meals of the day[6,**,††]

CYCLOSET® is a go-to option in your treatment toolbox to help with your patient's existing T2DM regimen[1]

*Study Design (CYCLOSET® monotherapy): A 24-week, multicenter, double-blind, placebo-controlled study. CYCLOSET® monotherapy, n=80; placebo, n=79. Premeal plasma glucose levels at Week 24: fasting: CYCLOSET®= -2 mg/dL, placebo= +28 mg/dL; lunch: CYCLOSET®= -16 mg/dL, placebo= +15 mg/dL; dinner: CYCLOSET®= -2 mg/dL, placebo= +13 mg/dL.[1,6,7]

†Study Design (CYCLOSET® + sulfonylurea): Two 24-week, multicenter, placebo-controlled, double-blind studies. The primary endpoint was reduction in HbA1c relative to placebo. Study K: CYCLOSET®, n=122; placebo, n=123. Study L: CYCLOSET®, n=122; placebo, n=127.[1,6]

‡Study Design (CYCLOSET® + 1-2 OADs): A 52-week, randomized, double-blind, multicenter, placebo-controlled safety study with subgroup efficacy assessments at Week 24. CYCLOSET® or placebo + 1 or 2 oral antidiabetic (OAD) medications (OADs included metformin, sulfonylurea, thiazolidinedione [TZD], alpha-glucosidase inhibitor, meglitinide, phenylalanine derivative); n=376; placebo, n=183. CYCLOSET® + metformin + sulfonylurea, n=177; placebo, n=90; CYCLOSET® + TZD ± OAD, n=78; placebo, n=44.[1,7,9-11]

§Study Design: Patients with T2DM on diet therapy alone and with poor glycemic control were randomized to treatment with CYCLOSET® or placebo (baseline fasting plasma glucose: 214 ± 6 and 203 ± 6 mg/dL, and HbA1c: 9.0 ± 0.1 and 8.8 ± 0.1, respectively) and administered standardized meals at breakfast, lunch, and dinner, before and 24 weeks following treatment. Plasma samples taken before and 1 and 2 hours after each meal were analyzed for glucose and insulin.[6]

‖A 2-way repeated measures (ANOVA) analysis of treatment and hour indicate a significant treatment effect over the entire diurnal (7 AM to 7 PM) period (P=0.0012). The change from baseline in 2-hour glucose level was significantly different for CYCLOSET® vs placebo at all 3 meals (P<0.05). The improvements in diurnal and postprandial glucose were not associated with an increase in insulin level measured at any of these test times.[6]

¶The American Association of Clinical Endocrinology recommends that blood pressure control be individualized; however, a target of <130/80 mm Hg is appropriate for most patients.[4]

#Study Design: Double-blind, 52-week, placebo-controlled, 2:1 CYCLOSET® to placebo randomized, outpatient, noninferiority safety study in 3070 patients with T2DM. CYCLOSET®, n=2054; placebo, n=1016. Primary outcome measures were incidence of serious adverse events and a composite endpoint of cardiovascular events. Baseline CYCLOSET® systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 130/78 mm Hg. Baseline placebo SBP/DBP were 130/77 mm Hg.[8]

**Mean baseline triglyceride levels of 250 mg/dL and free fatty acid levels of 800 µEq/L.[7]

††Secondary efficacy endpoint of the two 24-week efficacy studies as adjunct to stable sulfonylurea.[6,7]

IMPORTANT SAFETY INFORMATION *(continued)*

Orthostatic Hypotension/Syncope

- CYCLOSET can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation. Use caution in patients taking antihypertensive medications. Orthostatic vital signs should be assessed prior to initiation of CYCLOSET and periodically thereafter.
- Advise patients during early treatment to avoid situations that could lead to injury if syncope were to occur, and to make slow postural changes.

Psychotic Disorders

- The use of CYCLOSET in patients with severe psychotic disorders is not recommended.

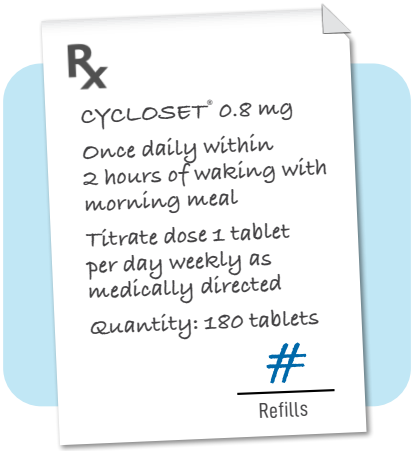
Impulse Control/Compulsive Behaviors

- Consider dose reduction or discontinuation of CYCLOSET if a patient develops intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably and/or other intense urges.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

ONCE-DAILY DOSING FOR ADDED GLYCEMIC CONTROL[1]

- CYCLOSET® is available in 0.8 mg tablets for dosing control as you gradually titrate to help patients adjust to therapy and reach their targeted therapeutic effects[1]



WEEK	# OF TABLETS PER DAY
WEEK 1	1
WEEK 2	2
WEEK 3	3
WEEK 4	4
Recommended dose of CYCLOSET® is 2 to 6 tablets a day, titrated until the maximal tolerated number of tablets is reached.[1,6]	
WEEK 5	5 (AS NEEDED)
WEEK 6	6 (AS NEEDED)

ACTUAL SIZE

- CYCLOSET® should be taken once daily, with food, within 2 hours of waking[1]
- If the morning dose is missed, instruct patients to skip the day and take their dose the next morning[1]

Help eligible patients save on their CYCLOSET® prescriptions

CYCLOSET® Savings Program

AS LITTLE AS

$0 CO-PAY FOR COMMERCIALLY ELIGIBLE PATIENTS*

Visit cycloset.com/savings to activate card

*Maximum benefits and other restrictions apply. See co-pay card for Eligibility Terms and Conditions.

IMPORTANT SAFETY INFORMATION *(continued)*

Somnolence

- CYCLOSET may cause somnolence, particularly when initiating therapy. Advise patients not to drive or operate heavy machinery if symptoms of somnolence occur.

Concomitant Use of Dopamine Antagonists or Agonists

- Concomitant use with dopamine antagonists, such as neuroleptic agents, may diminish the effectiveness of both drugs and is not recommended.
- Effectiveness and safety are unknown in patients already taking dopamine receptor agonists for other indications and concomitant use is not recommended.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

CYCLOSET®
bromocriptine mesylate tablets

ONCE CYCLOSET® HAS BEEN PRESCRIBED, A PRIOR AUTHORIZATION (PA) MAY BE NEEDED

Submitting a PA can be simple

1. Provide patient and insurance information
2. Include prescriber information (eg, practice name, your name, NPI #, DEA/license #)
3. Provide accurate information, including
   - **Age, diagnosis, dosing**–age of patient, T2DM, CYCLOSET® 0.8 mg tablet (taken orally once daily)[1]
   - **Previous therapies tried and failed**–eg, metformin and sulfonylurea
   - **ICD-10 code* for T2DM**–E11.9 type 2 diabetes mellitus without complications
   - **Rationale for prescribing CYCLOSET®**
4. Remember to include your signature and the date

ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.
*The ICD-10-CM code and all other patient access-related information are provided for informational purposes only. It is the treating physician's responsibility to determine the proper diagnosis, treatment, and applicable ICD-10-CM code. Salix Pharmaceuticals does not guarantee coverage or reimbursement for the product.

IMPORTANT SAFETY INFORMATION *(continued)*

Risks in Postpartum Patients

- CYCLOSET is contraindicated in postpartum patients. Serious and life-threatening adverse reactions have been reported in postpartum women who were administered bromocriptine for inhibition of lactation. These risks may be higher in postpartum patients with cardiovascular disease. The indication for use of bromocriptine for inhibition of postpartum lactation was withdrawn from bromocriptine-containing products and is not approved for CYCLOSET.

Safety and Effectiveness in Pediatrics

- The safety and effectiveness of CYCLOSET in pediatric patients have not been established.

Adverse Reactions

- In clinical trials, the most common adverse reactions reported in ≥5% of patients treated with CYCLOSET, and reported more commonly than in patients treated with placebo, included nausea, fatigue, dizziness, vomiting, and headache. Postmarketing reports with higher doses of bromocriptine used for other indications include psychotic disorders, hallucinations, and fibrotic complications.

Drug Interactions

- May increase the unbound fraction of highly protein-bound therapies, altering their effectiveness and safety profiles.
- May increase ergot-related side effects or reduce ergot effectiveness for migraines if co-administered within 6 hours of ergot-related drugs.
- Extensively metabolized by CYP3A4. Limit CYCLOSET dose to 1.6 mg/day during concomitant use of moderate CYP3A4 inhibitors. Avoid concomitant use of CYCLOSET with strong CYP3A4 inhibitors.

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

References: 1. CYCLOSET [prescribing information]. Tiverton, RI: VeroScience LLC. **2.** Chamarthi B, Vinik A, Ezrokhi M, Cincotta AH. Circadian-timed quick-release bromocriptine lowers elevated resting heart rate in patients with type 2 diabetes mellitus. *Endocrinol Diabetes Metab.* 2020;3(1):e00101. **3.** American Diabetes Association. Standards of medical care in diabetes—2021 abridged for primary care providers. *Clin Diabetes.* 2021;39(1):14-43. **4.** Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm–2020 executive summary. *Endocr Pract.* 2020;26(1):107-139. **5.** Licht CM, Vreeburg SA, van Reedt Dortland AK, et al. Increased sympathetic and decreased parasympathetic activity rather than changes in hypothalamic-pituitary-adrenal axis activity is associated with metabolic abnormalities. *J Clin Endocrinol Metab.* 2010;95(5):2458-2466. **6.** Data on file. Salix Pharmaceuticals. **7.** Cincotta AH, Meier AH, Cincotta M Jr. Bromocriptine improves glycaemic control and serum lipid profile in obese type 2 diabetic subjects: a new approach in the treatment of diabetes. *Expert Opin Investig Drugs.* 1999;8(10):1683-1707. **8.** Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care.* 2010;33(7):1503-1508. **9.** Florez H, Scranton R, Farwell WR, et al. Randomized clinical trial assessing the efficacy and safety of bromocriptine-QR when added to ongoing thiazolidinedione therapy in patients with type 2 diabetes mellitus. *J Diabetes Metab.* 2011;2(7):1-8. **10.** Vinik AI, Cincotta AH, Scranton RE, et al. Effect of bromocriptine-QR on glycemic control in subjects with uncontrolled hyperglycemia on one or two oral anti-diabetes agents. *Endocr Pract.* 2012;18:931-943. **11.** Scranton RE, Gaziano JM, Rutty D, Ezrokhi M, Cincotta A. A randomized, double-blind, placebo controlled trial to assess safety and tolerability during treatment of type 2 diabetes with usual diabetes therapy and either Cycloset™ or placebo. *BMC Endocr Disord.* 2007;7(1):3.

Salix Pharmaceuticals

CYCLOSET®
bromocriptine mesylate tablets