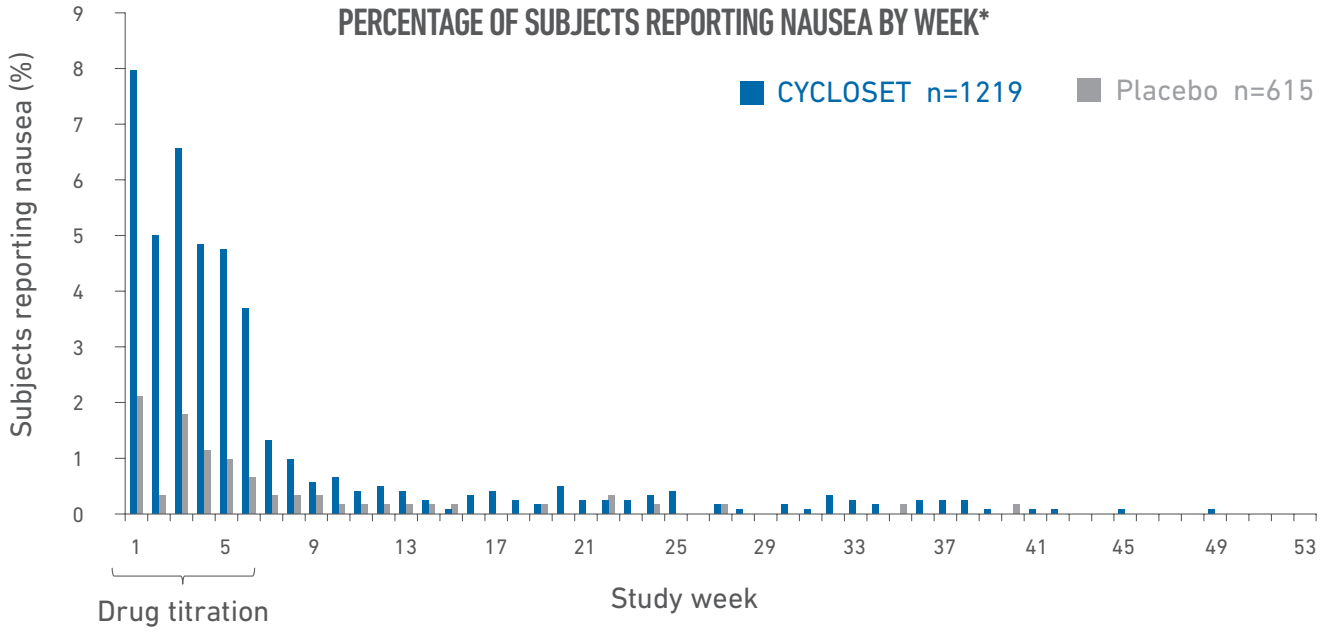
UNDERSTANDING CYCLOSET'S SAFETY PROFILE

Post-hoc Subgroup Analysis of Patients with HbA1c ≤7% and Well-controlled Type 2 Diabetes Mellitus in a 52-week safety trial

CYCLOSET® bromocriptine mesylate tablets

NAUSEA OCCURRED PRIMARILY DURING THE 6-WEEK FORCED TITRATION PERIOD[1,2]

Data from the double-blind, placebo-controlled, 52-week CYCLOSET safety trial among the subgroup with HbA1c ≤ 7.0% (CYCLOSET n=1219; placebo n=615). Dosing: Forced titration of 0.8 mg CYCLOSET per week increase until a maximum tolerated daily dose of 1.6 mg to 4.8 mg/day is achieved.[1]



Nausea associated with Cycloset treatment was more likely to occur during the initial 6 week forced titration period. In this subgroup of patients, nausea was reported in 31.7% of CYCLOSET subjects vs 8.0% of placebo subjects.[1] In the 52-week safety trial, of 3070 subjects with type 2 diabetes mellitus and a mean baseline HbA1c of 7.0%, nausea was reported in 32.2% of CYCLOSET subjects vs 7.6% of placebo subjects.[2] The severity of nausea was mild to moderate in >90% of cases.[1] The most common adverse event that led to discontinuation in the 52-week study was nausea (7.6% vs 1% placebo).[2]

*Subjects with baseline HbA1c ≤7.0% derived from the CYCLOSET Safety Trial.[2] Adverse event data are similar to those reported for the entire study population in the CYCLOSET Safety Trial.[1]

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.

IMPORTANT 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

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.

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 anti-hypertensive 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.

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.

Risk 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. Chamarthi B, Gaziano JM, Blonde L, et al. Timed bromocriptine-QR therapy reduces progression of cardiovascular disease and dysglycemia in subjects with well-controlled type 2 diabetes mellitus. *J Diabetes Res.* 2015;2015:157698. **2.** CYCLOSET [prescribing information]. Tiverton, RI: VeroScience, LLC.

Salix Pharmaceuticals

CYCLOSET®
bromocriptine mesylate tablets