CYCLOSET (bromocriptine mesylate)

- Psychosis: May exacerbate psychotic disorders or reduce the effectiveness of drugs that treat psychosis. Use in patients with severe psychotic disorders is not recommended. (5.2)
- Somnolence: May cause somnolence. Advise patients not to operate heavy machinery if symptoms of somnolence occur. (5.3)
- Interaction with dopamine antagonists: Concomitant use with dopamine antagonists such as neuroleptic agents may diminish the effectiveness of both drugs. Concomitant use is not recommended. (5.4, 7)
- Other dopamine receptor agonists: Effectiveness and safety are unknown in patients already taking dopamine receptor agonists for other indications. Concomitant use is not recommended. (5.5)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with CYCLOSET or any other antidiabetic drug. CYCLOSET does not increase the risk of macrovascular events. (5.6, 6.1)

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1.2 Important Limitations of Use

2 DOSAGE AND ADMINISTRATION

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CYCLOSET safely and effectively. See full prescribing information for CYCLOSET.

CYCLOSET® (bromocriptine mesylate tablets), for oral use

Initial U.S. Approval: 1978

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Dosage and Administration

- Taken within two hours after waking in the morning with food (2.1)
- Initial dose is one tablet (0.8 mg) daily increased weekly by one tablet until maximal tolerated daily dose of 1.6 to 4.8 mg is achieved. (2.2)
- Limit dose to 1.6 mg daily during concomitant use of a moderate CYP3A4 inhibitor. Avoid concomitant use with strong CYP3A4 inhibitors. (2.3)

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CONTRAINDICATIONS

- Do not use in patients with hypersensitivity to ergot-related drugs, bromocriptine or to any of the excipients in CYCLOSET. (4)
- Do not use in patients with syncopal migraines. May precipitate hypotension. (4)
- Do not use in nursing women. May inhibit lactation. Postmarketing reports of stroke in this patient population. (4, 6.2, 6.3)

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WARNINGS AND PRECAUTIONS

- Hypotension: Can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation. Use caution in patients taking antihypertensive medications. Assess orthostatic vital signs prior to initiation of CYCLOSET and periodically thereafter. Advise patients during early treatment to avoid situations that could lead to injury if syncope was to occur. (5.1, 6.1)

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ADVERSE REACTIONS

- Somnolence: May cause somnolence. Advise patients not to operate heavy machinery if symptoms of somnolence occur. (5.3)
- Interaction with dopamine antagonists: Concomitant use with dopamine antagonists such as neuroleptic agents may diminish the effectiveness of both drugs. Concomitant use is not recommended. (5.4, 7)
- Other dopamine receptor agonists: Effectiveness and safety are unknown in patients already taking dopamine receptor agonists for other indications. Concomitant use is not recommended. (5.5)
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with CYCLOSET or any other antidiabetic drug. CYCLOSET does not increase the risk of macrovascular events. (5.6, 6.1)

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DRUG INTERACTIONS

- May increase the unbound fraction of highly protein-bound therapies, altering their effectiveness and safety profiles. (7)
- May increase ergot-related side effects or reduce ergot effectiveness for migraines if co-administered within 6 hours of ergot-related drugs. (7)
- 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. (2.3, 7)
Women who are nursing their children, CYCLOSET may inhibit lactation. There are no postmarketing reports of stroke in this patient population although causality has not been proven [see Use in Specific Populations (8.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

Hypotension, including orthostatic hypotension, can occur, particularly upon initiation of CYCLOSET therapy and with dose escalation. In a 52-week, randomized clinical trial of 3070 patients, hypotension was reported in 2.2% of patients randomized to CYCLOSET compared to 0.8% of patients randomized to placebo. Among CYCLOSET-treated patients reporting symptomatic hypotension, 98% were on at least one blood pressure medication compared to 73% on such medication in the total study population. In this trial, six CYCLOSET-treated patients (0.3%) reported an adverse event of orthostatic hypotension compared to 2 (0.2%) placebo–treated patients. All six patients were taking antihypertensive medications. Hypotension can result in syncope. In this trial, syncope due to any cause was reported in 1.6% of CYCLOSET-treated patients and 0.7% of placebo-treated patients [see Adverse Reactions (6.1)]. As a precaution, assessment of orthostatic vital signs is recommended prior to initiation of CYCLOSET and periodically thereafter. During early treatment with CYCLOSET, patients should be advised to make slow postural changes and to avoid situations that could lead to serious injury if syncope was to occur. Use caution in patients taking antihypertensive medications.

5.2 Psychotic Disorders

In patients with severe psychotic disorders, treatment with a dopamine receptor agonist such as CYCLOSET may exacerbate the disorder or may diminish the effectiveness of drugs used to treat the disorder. Therefore, the use of CYCLOSET in patients with severe psychotic disorders is not recommended.

5.3 Somnolence

CYCLOSET may cause somnolence. In a 52-week, randomized clinical trial, 4.3% of CYCLOSET-treated patients and 1.3% of placebo–treated patients reported somnolence as an adverse event. None of these events were reported as serious, and the majority of patients reported resolution of somnolence over time. Patients should be made aware of this potential side effect, particularly when initiating therapy with CYCLOSET. Patients experiencing somnolence should refrain from driving or operating heavy machinery.

5.4 Interaction with Dopamine Receptor Antagonists

Dopamine receptor antagonists, including neuroleptic agents that have dopamine D2 receptor antagonist properties (e.g., clozapine, olanzapine, ziprasidone), may reduce the effectiveness of CYCLOSET, and CYCLOSET may reduce the effectiveness of these agents. CYCLOSET has not been studied in patients taking neuroleptic drugs. The concomitant use of CYCLOSET and dopamine receptor antagonists, including neuroleptic drugs, is not recommended.

5.5 Other Dopamine Receptor Agonists

Other dopamine receptor agonists are indicated for the treatment of Parkinson’s disease, hyperprolactinemia, restless leg syndrome, acromegaly, and other disorders. The effectiveness and safety of CYCLOSET in patients who are already taking one of these other dopamine receptor agonists is unknown. Concomitant use is not recommended.

5.6 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with CYCLOSET or any other antidiabetic drug. In a 52-week, randomized clinical trial, CYCLOSET use was not associated with an increased risk for adverse cardiovascular events [see Adverse Reactions (6.1)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice. In the pooled CYCLOSET Phase 3 clinical trials (CYCLOSET N = 2,296; placebo N = 1,266), adverse events leading to discontinuation occurred in 539 (24%) CYCLOSET–treated patients and 118 (9%) placebo–treated patients. This between-group difference was driven mostly by gastrointestinal adverse events, particularly nausea.

The CYCLOSET safety trial was a 52-week, placebo-controlled study that included patients treated only with diet therapy or with other antidiabetic medications. A total of 3,070 patients were randomized to CYCLOSET (titrated to 1.6 to 4.8 mg daily, as tolerated) or placebo. The study population had a mean baseline age of 60 years (range 27-80) and 33% were 65 years of age or older. Approximately 43% of the patients were female, 68% were Caucasian, 17% were Black, 13% were Hispanic, and 1% were Asian. The mean baseline body mass index was 32 kg/m². The mean duration of diabetes at baseline was 8 years and the mean baseline HbA1c was 7.0% with a mean baseline fasting plasma glucose of 142 mg/dL. At baseline, 12% of patients were treated with diet only, 40% were treated with one oral antiabetic agent, 33% were treated with two oral antidiabetic agents, and 16% were treated with insulin alone or insulin in combination with an oral antidiabetic agent. At baseline, 76% of patients reported a history of hypercholesterolemia, 75% reported a history of hypertension, 11% reported a history of revascularization surgery, 10% reported a history of myocardial infarction, 10% reported a history of angina, and 5% reported a history of stroke. Forty-seven percent of the CYCLOSET–treated patients and 32% of the placebo–treated patients prematurely discontinued treatment. Adverse events leading to discontinuation of study drug occurred among 24% of the CYCLOSET–treated patients and 15% of the placebo–treated patients. This between-group difference was driven mostly by gastrointestinal adverse events, particularly nausea.

Table 1 summarizes the adverse events reported in ≥5% of patients treated with CYCLOSET in the Phase 3 clinical trials regardless of investigator assessment of causality. The most commonly reported adverse events (nausea, fatigue, vomiting, headache, dizziness) lasted a median of 14 days and were more likely to occur during the initial titration of CYCLOSET. None of the reports of nausea or vomiting were described as serious. There were no differences in the pattern of common adverse events across race or age groups (<65 years old vs. >65 years old). In the 52-week CYCLOSET safety trial, 11.5% of CYCLOSET–treated women compared to 3.6% of placebo–treated women reported vomiting. In this same trial, 5.4% of CYCLOSET–treated men compared to 2.8% of placebo–treated men reported vomiting.

Table 1: Adverse Events Reported in Phase 3 Clinical Trials of CYCLOSET (>5% of Patients and Numerically More Frequent in CYCLOSET–Treated Patients than in Placebo–Treated Patients, Regardless of Investigator Assessment of Causality)

<table>
<thead>
<tr>
<th>Event</th>
<th>CYCLOSET 1.6 mg - 4.8 mg N (%)</th>
<th>Placebo N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 159</td>
<td>N = 80</td>
<td>N = 79</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (32.5)</td>
<td>6 (7.6)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>11 (13.8)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (12.5)</td>
<td>7 (8.9)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10 (12.5)</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 (12.5)</td>
<td>6 (7.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (11.3)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>8 (10.0)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (8.8)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>6 (7.5)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6 (7.5)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (6.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (6.3)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (5.0)</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

5.2 Adjusted to Sulfonylurea (2 pooled 24-week studies)

<table>
<thead>
<tr>
<th>Event</th>
<th>CYCLOSET 1.6 mg - 4.8 mg N (%)</th>
<th>Placebo N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 494</td>
<td>N = 244</td>
<td>N = 250</td>
</tr>
<tr>
<td>Nausea</td>
<td>62 (25.4)</td>
<td>12 (4.8)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>46 (18.9)</td>
<td>20 (8.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>41 (16.8)</td>
<td>40 (16.0)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>23 (9.4)</td>
<td>19 (7.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>24 (9.8)</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Cold</td>
<td>20 (8.2)</td>
<td>20 (8.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>29 (11.9)</td>
<td>14 (5.6)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>26 (10.7)</td>
<td>12 (4.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>235 (11.4)</td>
<td>84 (8.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>285 (13.9)</td>
<td>68 (6.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>303 (14.8)</td>
<td>93 (9.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (5.3)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>13 (5.3)</td>
<td>6 (2.4)</td>
</tr>
</tbody>
</table>

5.3 52-Week Safety Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>CYCLOSET 1.6 mg - 4.8 mg N (%)</th>
<th>Placebo N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 3070</td>
<td>N = 2054</td>
<td>N = 1016</td>
</tr>
<tr>
<td>Nausea</td>
<td>661 (32.2)</td>
<td>77 (7.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>303 (14.8)</td>
<td>93 (9.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>285 (13.9)</td>
<td>68 (6.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>235 (11.4)</td>
<td>84 (8.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>167 (8.1)</td>
<td>32 (3.1)</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>167 (8.1)</td>
<td>81 (8.0)</td>
</tr>
</tbody>
</table>

5.4 Table 1 includes all randomized subjects receiving at least one dose of study drug

The Safety enrolled patients treated with diet or no more than 2 antidiabetic medications (metformin, insulin secretagogues such as a sulfonylurea, thiazolidinediones, alpha glucosidase inhibitors, and/or insulin).

Hypoglycemia

In the monotherapy trial, hypoglycemia was reported in 2 CYCLOSET–treated patients (3.7%) and 1 placebo–treated patient (1.3%). In the add–to–sulfonylurea trials, the incidence of hypoglycemia was 8.6% among the CYCLOSET–treated patients and 5.2% among the placebo–treated patients. In the CYCLOSET safety trial, hypoglycemia was...
defined as any of the following: 1) symptoms suggestive of hypoglycemia that promptly resolved with appropriate intervention, 2) symptoms with a measured glucose <80 mg/dL, or 3) measured glucose below 49 mg/dL regardless of symptoms. In the 52-week safety trial, the incidence of hypoglycemia was 6.9% among the CYCLOSET-treated patients and 5.3% among the placebo-treated patients. In the safety trial, severe hypoglycemia was defined as an inability to self-treat neurological symptoms consistent with hypoglycemia that occurred in the setting of a measured blood glucose <50 mg/dL (or evidence of prompt resolution of these symptoms with administration of oral carbohydrates, subcutaneous glucagon, or intravenous glucose if blood glucose was not measured). In this trial, severe hypoglycemia was reported among 0.5% of CYCLOSET-treated patients and 1% of placebo-treated patients.

Sycope
In combined Phase 2 and 3 clinical trials, sycope was reported in 1.4% of the 2,500 CYCLOSET-treated patients and 0.6% of the 1,454 placebo-treated patients. Among the 3,070 patients studied in the 52-week safety trial, 33 CYCLOSET-treated patients (1.6%) and 7 placebo-treated patients (0.7%) reported an adverse event of syncope. The cause of sycope is not known in all cases [see Warnings and Precautions (5.1)].

In this trial, electrocardiograms were not available at the time of these events, but an assessment of routine electrocardiograms obtained during the course of the trial did not identify arrhythmias or QTC interval prolongation among the CYCLOSET-treated patients reporting syncope.

Central Nervous System
In the 52-week safety trial, somnolence and hypotension were the only adverse events within the nervous system organ class that were reported at a rate of <5% and >1% and that occurred at a numerically greater frequency among CYCLOSET-treated patients (4.3% vs. placebo, 1.3% for somnolence; CYCLOSET 1.4% vs. placebo 1.1% for hypotension).

Serious Adverse Events and Cardiovascular Safety
The primary endpoint of the 52-week safety trial was the occurrence of all serious adverse events. A secondary endpoint was the occurrence of the composite of myocardial infarction, stroke, coronary revascularization, hospitalization for angina, and hospitalization for congestive heart failure.

All serious adverse events and cardiovascular endpoints were adjudicated by an independent event adjudication committee. Serious adverse events occurred in 176/2054 (8.5%) CYCLOSET-treated patients and 98/1016 (9.6%) placebo-treated patients. The hazard ratio comparing CYCLOSET to placebo for the time to first occurrence of a serious adverse event was 1.02 (upper bound of one-sided 96% confidence interval, 1.27). None of the serious adverse events in this study occurred more than 0.3 percentage points higher with CYCLOSET than with placebo. The composite cardiovascular endpoint occurred in 31 (1.5%) CYCLOSET-treated patients and 30 (3.0%) placebo-treated patients. The hazard ratio comparing CYCLOSET to placebo for the time to first occurrence of the prespecified composite cardiovascular endpoint was 0.58 (two-sided 95% confidence interval, 0.35–0.96). Therefore, the incidence of this composite endpoint was not increased with CYCLOSET relative to placebo.

6.2 Postmarketing Experience
The active ingredient in CYCLOSET (bromocriptine mesylate) has been used in other formulations and often multiple times per day to treat hyperprolactinemia, acromegaly, and Parkinson’s disease. There are no available reports of adverse reactions in patients with prolactinomas that have received CYCLOSET outside the setting of clinical trials. The occurrence of stroke in this patient population has not been proven. Based on the CYCLOSET clinical trials, there is no evidence of increased risk for stroke when CYCLOSET is used to treat type 2 diabetes.

Neuroleptic-Like Malignant Syndrome
A neuroleptic-like malignant syndrome (manifested by high fever and increase in creatine kinase) has been reported upon cessation of bromocriptine treatment in patients with advanced Parkinson’s disease or patients with secondary Parkinsonism. To date, there have been no reported cases of neuroleptic-like malignant syndrome in combined Phase 2 and 3 controlled clinical trials of CYCLOSET, including the Safety Trial (N = 2500). In the CYCLOSET Safety Trial, there were no reports of neuroleptic-like malignant syndrome during the 30 days of follow-up after cessation of CYCLOSET (N = 2054).

7 DRUG INTERACTIONS
The active ingredient in CYCLOSET (bromocriptine mesylate) is highly bound to serum proteins. Therefore, CYCLOSET may increase the unbound fraction of other concomitantly used highly protein-bound therapies (e.g., salicylates, sulfonamides, chloroquine and propranolol), which may alter their effectiveness and risk for side effects.

CYCLOSET is a dopamine receptor agonist. Concomitant use of dopamine receptor antagonists, such as neuroleptics (e.g., phenothiazines, butyrophenones, thioxanthenes), or metoclopramide may diminish the effectiveness of CYCLOSET, and CYCLOSET may diminish the effectiveness of these other therapies. The concurrent use of CYCLOSET with these agents has not been studied in clinical trials and is not recommended [see Warnings and Precautions (5.4)].

CYCLOSET in combination with ergot-related drugs may cause an increase in the occurrence of ergot-related side effects, such as nausea, vomiting, and fatigue, and may also reduce the effectiveness of these ergot therapies when used to treat migraine. The concurrent use of these ergot agents within 6 hours of CYCLOSET dosing is not recommended.

CYCLOSET is extensively metabolized by the liver via CYP3A4. Therefore, potent inhibitors or inducers of CYP3A4 may increase or reduce the circulating levels of CYCLOSET, respectively. Use caution when co-administering drugs that are inhibitors or inducers of CYP3A4. CYCLOSET dose should not exceed 1.6 mg once daily concomitantly with a moderate CYP3A4 inhibitor (e.g., erythromycin).

Concomitant use of strong CYP3A4 inhibitors (e.g., azole antifungals, HIV protease inhibitors) with CYCLOSET should be avoided. Ensure adequate washout of the strong CYP3A4 inhibitor before initiating CYCLOSET treatment [see Clinical Pharmacology (12.3)].

There are postmarketing reports of hypertension and tachycardia when bromocriptine was co-administered with sympathomimetic drugs (e.g., phenylpropanolamine and isometheptene) in postpartum women. There are limited clinical trial data supporting the safety of co-administering sympathomimetic drugs and CYCLOSET for more than 10 days. Therefore, concomitant use of these agents with CYCLOSET for more than 10 days duration is not recommended. Also, there are limited clinical trial data supporting the safety of selective 5-hydroxytryptamine 1A (5-HT1A) agonists (e.g., sumatriptan) used concurrently with CYCLOSET, and the concomitant use of these agents with CYCLOSET should be avoided.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category B
Two strains of pregnant rats were dosed orally with 3, 10, and 30 mg/kg/day (up to 72 times the human 4.8 mg daily dose, based on mg/m² comparison) from gestation day 6-15 and with a single dose of 10 mg/kg on gestation day 5. Implantation was inhibited at 10 and 30 mg/kg (24 and 72 times the human 4.8 mg daily dose, based on mg/m² comparison). When rats were dosed with 3, 10, and 30 mg/kg/day from gestation day 6-15 there was an increase in resorptions at 10 and 30 mg/kg. These effects were probably due to the dependence of implantation and the maintenance of gestation on prolactin in the rat and are not relevant for humans in which these events are not dependent on prolactin but on luteinizing hormone. There was no evidence of teratogenic effects in the rat.

In a small study in macaque monkeys given oral doses of 2 mg/kg/day (10 times the human 4.8 mg daily dose, based on mg/m² comparison) during organogenesis no embryotoxic or teratologic effects were observed.

When male rats given oral doses of 2, 10, or 50 mg/kg/day (up to 120 times the human 4.8 mg daily dose, based on mg/m² comparison) were mated with untreated females, there was a slight increase in pup loss in the 10 and 50 mg/kg/day groups (24-120 times the human 4.8 mg daily dose, based on mg/m² comparison). In two strains of pregnant rabbits treated from gestation day 6-18 with oral doses of 3, 10, 30, 100, and 300 mg/kg/day (up to 1400 times the human 4.8 mg daily dose, based on mg/m² comparison) there was maternal toxicity and embryolethality at doses >10 mg/kg/day (48 times the human 4.8 mg daily dose, based on mg/m² comparison). Implantation was not affected in rabbits
CYCLOSET
(bromocriptine mesylate)

treated from gestation day 1-6 with oral doses of 100-300 mg/kg/day (480-1400 times the human 4.8 mg daily dose, based on mg/m² comparison).

Studies in pregnant women have not shown that bromocriptine increases the risk of abnormalities when administered during pregnancy. Information concerning 1,276 pregnancies in women taking bromocriptine has been collected. In the majority of cases, bromocriptine was discontinued within the first 8 weeks of pregnancy (mean 29 days); however, 8 patients received the drug continuously throughout pregnancy. The mean daily dose for all patients was 5.8 mg (range 1.40 mg). Of these 1,276 pregnancies, there were 1,088 full-term deliveries (4 stillborn), 145 spontaneous abortions (11.4%), and 28 induced abortions (2.2%). Twelve extrauterine gravidities and 3 hydatidiform moles (twice in the same patient) caused early termination of pregnancy. These data compare favorably with the abortion rate (11-25%) cited for pregnancies induced by clomiphene citrate, menopausal gonadotropin, and chorionic gonadotropin. Although spontaneous abortions often go unreported, especially prior to 20 weeks of gestation, their frequency has been estimated to be 10-15% in the general population. The incidence of birth defects in the general population ranges from 2-4.5%. The incidence of birth defects in 1,109 live births from patients receiving bromocriptine was 3.3%. There is no suggestion that bromocriptine contributed to the type or incidence of birth defects in this group of infants.

A review of 4 different multicenter surveillance programs analyzed 2,351 pregnancies of 2,185 women treated with bromocriptine. In 583 children born of these women and followed for a minimum of 3-12 months, there was no suggestion of any adverse effect of intra-uterine exposure to bromocriptine on postnatal development. Most (75%) women who had been treated over 8 weeks. In 86% women having 93 pregnancies and treated with bromocriptine throughout pregnancy or from week 30 of pregnancy onwards (mostly for treatment of prolactinoma), there was only 1 spontaneous abortion. Similar results have been obtained in a Japanese hospital survey of 4824 children born to 434 patients treated with bromocriptine during pregnancy and followed for at least one year. Because the studies in humans cannot rule out the possibility of harm, CYCLOSET should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

CYCLOSET is contraindicated in women who are nursing their children. CYCLOSET contains bromocriptine which inhibits lactation. The indication for use of bromocriptine for inhibition of postpartum lactation was withdrawn based on postmarketing reports of stroke in this setting [see Contraindications (4), Adverse Reactions (6.2)].

8.4 Pediatric Use

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

8.5 Geriatric Use

In the two clinical trials of CYCLOSET add-on to sulfonylurea therapy and in the monotherapy trial, a total of 54 patients randomized to CYCLOSET were ≥65 years old. In the 52-week safety trial, 601 of the 2,054 CYCLOSET-treated patients (29%) were ≥65 years old. No overall differences in safety or effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. [See Clinical Studies (14).]

10 OVERDOSAGE

With another formulation of bromocriptine mesylate, the most commonly reported signs and symptoms associated with acute overdose were nausea, vomiting, constipation, diarrhoea, dizziness, pallor, severe hypotension, malaise, confusion, lethargy, drowsiness, delusions, hallucinations, and repetitive yawning. The lethal dose has not been established.

Treatment of overdose consists of removal of the drug by emesis (if conscious), gastric lavage, activated charcoal, or saline catharsis. Careful supervision and recording of fluid intake and output is essential. Hypotension should be treated by placing the patient in the Trendelenburg position and administering intravenous fluids. If satisfactory relief of hypotension cannot be achieved by using the above measures to their fullest extent, vasopressors should be considered.

11 DESCRIPTION

CYCLOSET Tablets contain micronized bromocriptine mesylate, a dopamine receptor agonist. Bromocriptine mesylate is chemically designated L-Dopa-D-tyrosine 2-bromo-12'-hydroxy-2'- (1-methylethyl)-5'-(2-methylpropyl)-, monomethanesulfonate (salt), (5α)-. CYCLOSET is a single enantiomer with absolute configuration 5R, 9R, 2'R, 5'S, 11'S, 12'S.

The structural formula of bromocriptine is shown below:

CYCLOSET Tablets contain bromocriptine mesylate, a dopamine receptor agonist. Bromocriptine mesylate is a white or slightly colored micronized crystalline powder with a molecular formula of C_{32}H_{40}BrN_{5}O_{5} ∙CH_{4}SO_{3} and a molecular weight of 750.72. CYCLOSET Tablets contain bromocriptine mesylate USP in an amount equivalent to 0.8 mg. of bromocriptine. Each tablet contains the following inactive ingredients: lactose, corn starch, magnesium stearate, colloidal silicon dioxide, and citric acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CYCLOSET contains bromocriptine mesylate, a sympatholytic, dopamine D2 receptor agonist. In patients with type 2 diabetes, timed morning administration of CYCLOSET is associated with increased insulin sensitivity and glucose disposal and reduced fasting and postprandial hyperglycemia throughout the meals of the day without raising plasma insulin levels.

12.2 Pharmacodynamics

Postprandial Glucose and Insulin Response to a Meal

Patients with type 2 diabetes and inadequate glycemic control on diet alone were randomized to CYCLOSET or placebo in a 24-week monotherapy clinical trial. At baseline and study end, plasma samples for insulin and glucose were obtained before and 1 hour, and 2 hours after standardized meals for breakfast, lunch, and dinner. In this trial, once-daily (8 a.m.) CYCLOSET improved postprandial glucose without increasing plasma insulin concentrations.

9-Medicated Glucose Disposal

Patients with type 2 diabetes and inadequate glycemic control on sulfonylurea therapy were randomized to CYCLOSET or placebo in a 16-week clinical trial. In this trial CYCLOSET therapy improved insulin-mediated glucose disposal and glucose tolerance and resulted in lower plasma glucose and HbA1c levels.

12.3 Pharmacokinetics

Absorption and Bioavailability

When administered orally, approximately 65-95% of the CYCLOSET dose of bromocriptine mesylate is absorbed. Due to extensive first-pass metabolism, approximately 7% of the dose reaches the systemic circulation. Under fasting conditions the time to maximum plasma concentration is 53 minutes. In contrast, following a standard high-fat meal, the time to maximum plasma concentration is increased to approximately 90-120 minutes. Also, the relative bioavailability of CYCLOSET is increased under fed conditions as compared to fasting conditions by an average of approximately 55-65% (increase in AUC).
In Vivo Assessment

The concomitant use of macrolide antibiotics such as erythromycin (250 mg four times a day), a known inhibitor of CYP3A4, along with bromocriptine (5 mg) was shown to increase the AUC (2.8-fold) and C_{max} (4.6-fold) of bromocriptine [see Dosage and Administration (2.3), Drug Interactions (7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 74-week dietary study in mice at doses up to 50 mg/kg/day (56 times the human 4.8 mg daily dose, based on mg/m² comparison), there was no evidence of tumorigenicity. In a 100-week dietary carcinogenicity study in rats at doses of 1.8, 9.9 and 44.5 mg/kg/day (up to 106 times the human 4.8 mg daily dose, based on mg/m² comparison), there was a significant increase in the incidence of malignant uterine neoplasms in the mid- and high-dose groups (24-106 times the human 4.8 mg daily dose, based on mg/m² comparison). The increase in uterine neoplasms was probably due to the inhibition of prolactin-stimulated progesterone secretion resulting in estrogen domination and endometrial stimulation in the aging rat. Because prolactin does not play a role in human progestosterone production this finding is unlikely to be clinically relevant.

Mutagenicity

Bromocriptine was not mutagenic in the in vitro Ames bacterial mutation assay, the V79 Chinese hamster fibroblast mutagenicity test, the in vivo bone marrow micronucleus test in mice and the in vivo Chinese hamster bone marrow chromosomal aberration test.

14 CLINICAL STUDIES

A total of 3,723 patients with type 2 diabetes were randomized across 4 double-blind, placebo-controlled clinical trials conducted to evaluate the safety and glycemic efficacy of CYCLOSET. In the pooled 24-week monotherapy trial and the two 24-week add-on to sulfonylurea trials (N = 653), the mean age of the CYCLOSET-treated patients (N = 324) was 55 years, 71% were male and 73% Caucasian. In the 52-week safety trial (N = 3,070), the mean age for the entire study population was 60 years and 43% of patients were female, 68% were Caucasian, 17% were Black, 13% were Hispanic, and 1% were Asian. In all 4 clinical trials, patients assigned to treatment with CYCLOSET received an initial dose of 0.8 mg, which was increased by 0.8 mg each week for 6 weeks (4.8 mg/day final dose) if no intolerance occurred or until the maximum tolerated dose ≥1.6 mg/day was reached. In patients with type 2 diabetes, treatment with CYCLOSET produced clinically significant improvements in HbA1c and postprandial glucose (PPG).

14.1 Monotherapy

A total of 159 overweight (body mass index ≥26.0 kg/m² for males and ≥28.0 kg/m² for females) adults with type 2 diabetes and inadequate glycemic control (HbA1c 7.5-11%) participated in a 24-week, placebo-controlled, monotherapy trial that evaluated the efficacy and safety of CYCLOSET as an adjunct to diet and exercise. Mean body weight at baseline was 93 kg in the CYCLOSET group and 96 kg in the placebo group. Mean HbA1c at baseline was 9.0% in the CYCLOSET group and 8.6% in the placebo group. Mean duration of diabetes at baseline was 5 years in the CYCLOSET group and 4 years in the placebo group. Of the 80 patients in the CYCLOSET group, 69% (N = 55) achieved the maximum daily dose of 4.8 mg. CYCLOSET improved HbA1c and fasting plasma glucose compared to placebo (Table 2). Mean change from baseline in body weight was +0.2 kg in the CYCLOSET group (N = 78) and +0.5 kg in the placebo group (N = 77).

Table 2: Changes in Glycemic Parameters in a 24-Week Placebo-Controlled Study of CYCLOSET as Monotherapy in Patients with Type 2 Diabetes†

<table>
<thead>
<tr>
<th>Study 1</th>
<th>CYCLOSET Add-on to Sulfonylurea</th>
<th>Placebo Add-on to Sulfonylurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 114</td>
<td>N = 112</td>
<td>N = 113</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>-0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Change from baseline (adj. mean)</td>
<td>-0.5**</td>
<td>-0.6*</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>216</td>
<td>227</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Change from baseline (adj. mean)</td>
<td>-18**</td>
<td>-20**</td>
</tr>
</tbody>
</table>

† intent-to-treatment population using last observation carried forward between-group change from baseline in HbA1c

P-value calculated by ANOVA; *p = 0.001, **p = 0.006

14.2 Combination Therapy

CYCLOSET Add-on to Sulfonylurea Therapy

Patients with type 2 diabetes and inadequate glycemic control (HbA1c 7.8-12.5%) on sulfonylurea therapy (mean HbA1c 9.4%) participated in Study L, a 24-week, randomized, double-blind, placebo-controlled trial that evaluated the safety and glycemic efficacy of CYCLOSET when added to stable sulfonylurea therapy. The mean duration of diabetes was 6 years in the CYCLOSET group and 6 years in the placebo group. The range of body mass index was 26-40 kg/m² for men and 28-40 kg/m² for women, with a mean of 32 kg/m² in both treatment groups. Of the 122 patients in the CYCLOSET group, 83 (68%) achieved the maximum dose of study drug. The mean change from baseline in body weight was +0.9 kg in the CYCLOSET group and +0.5 kg in the placebo group.

In another similarly designed trial, Study K, patients with type 2 diabetes and inadequate glycemic control (HbA1c 7.8-12.5%) on stable sulfonylurea therapy were randomized to add-on therapy with either CYCLOSET (N = 122) or placebo (N = 123). The range of body mass index was 26-40 kg/m² for men and 28-40 kg/m² for women, with a mean of 32 kg/m² in the CYCLOSET group and 33 kg/m² in the placebo group. Of the 122 patients in the CYCLOSET group, 91 (75%) achieved the maximum dose of study drug. Mean change from baseline in body weight was +1.4 kg in the CYCLOSET group and +0.5 kg in the placebo group. CYCLOSET improved HbA1c and fasting blood glucose concentrations compared to placebo (Table 3).

Table 3: Changes in Glycemic Parameters for CYCLOSET Versus Placebo in Two Add-on to Sulfonylurea Trials

<table>
<thead>
<tr>
<th>Study 1</th>
<th>CYCLOSET Add-on to Sulfonylurea</th>
<th>Placebo Add-on to Sulfonylurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 122</td>
<td>N = 123</td>
<td>N = 127</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>-0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Change from baseline (adj. mean)</td>
<td>-0.5**</td>
<td>-0.6*</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>216</td>
<td>227</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Change from baseline (adj. mean)</td>
<td>-18**</td>
<td>-20**</td>
</tr>
</tbody>
</table>

1 intent-to-treatment population using last observation carried forward between-group change from baseline in HbA1c

P-value calculated by ANOVA; *p = 0.001, **p = 0.006
Table 4: Changes in HbA1c from Baseline to Week 24 in the CYCLOSET Safety Trial Subgroup of Patients with Type 2 Diabetes and Inadequate Glycemic Control (Baseline HbA1c ≥7.5%) on 1-2 Oral Antidiabetic Medications†

<table>
<thead>
<tr>
<th>Adjunct to 1-2 Oral Antidiabetic Medications</th>
<th>24-Week Intent-to-Treat</th>
<th>CYCLOSET</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 376</td>
<td>N = 183</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>8.3</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.4</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>-0.5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Patients achieving HbA1c ≤7.0</td>
<td>25</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Adjunct to Metformin + Sulfonylurea Only‡</td>
<td>N = 177</td>
<td>N = 90</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>8.3</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.5</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>-0.5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Patients achieving HbA1c ≤7.0</td>
<td>27</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

† Intent-to-treat population using last observation carried forward between-group change from baseline in HbA1c

P-value is based on an ANCOVA model with treatment and center as fixed effects, and baseline HbA1c as covariates; *p<0.001

‡ Patients in the “metformin + sulfonylurea only” subgroup are also counted in the baseline HbA1c as covariates; *p<0.001

14.3 Changes in Lipids and Blood Pressure
CYCLOSET has not demonstrated an unfavorable hypertensive effect on blood pressure. Hypotension has been reported with use of CYCLOSET in clinical trials (see Warnings and Precautions (5.1)).

16 HOW SUPPLIED/STORAGE AND HANDLING
CYCLOSET 0.8 mg tablets are WHITE and round with “C” on one side and “9” on the other. The tablets are supplied as follows:
NDC 68012-258-20 unit-of-use bottles of 200
NDC 68012-258-21 unit-of-use bottles of 21 (samples only).

Storage
Store and dispense: At 20-25°C (68-77°F) in a tight, light-resistant container. See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information). Patients should be informed of the potential risks and benefits of CYCLOSET and of alternative therapies. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, and diaphoresis. Hypotension and syncope may occur more frequently during initial therapy or with an increase in dose at any time. During early treatment with CYCLOSET, patients should be advised to make slow postural changes and to avoid situations that could predispose to serious injury if syncope was to occur.

Patients should be advised that CYCLOSET may cause somnolence. Advise patients not to operate heavy machinery if symptoms of somnolence occur.

Women who are nursing their children should be advised to not take CYCLOSET.

Physicians should instruct their patients to read the Patient Package Insert before starting CYCLOSET therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their healthcare provider if they develop any unusual symptoms or if any known symptom persists or worsens.

Manufactured for:
VeroScience, LLC
Tiverton, RI 02878 USA

Distributed by:
Salix Pharmaceuticals, a division of
Bausch Health US, LLC
Bridgewater, NJ 08807 USA

Printed in USA
For information for healthcare professionals, call 1-800-321-4576.
For patent information: http://veroscience.com/products/patents.html

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How should I take CYCLOSET?
• Take CYCLOSET exactly as your healthcare provider tells you to take it.
• Take CYCLOSET by mouth each day.
• Take CYCLOSET with food.
• Take CYCLOSET within 2 hours after waking in the morning.
• If you miss your morning dose, wait until the next morning to take your medication.
• Do not take a double dose of CYCLOSET.
• During periods of stress on the body, such as fever, trauma, infection, or surgery, your medication needs may change. Contact your healthcare provider right away.
• If you take too much CYCLOSET, call your healthcare provider or go to the nearest emergency department right away.
• While taking CYCLOSET:
  o check your blood sugar as your healthcare provider tells you to stay on your prescribed diet and exercise program
  o learn to prevent, recognize, and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes
  o see your healthcare provider for regular blood tests, including your blood sugar levels and hemoglobin HbA1c

What are the possible side effects of CYCLOSET?
CYCLOSET may cause serious side effects, including:
• Low blood pressure
• Fainting
• Severe dizziness which can be caused by postural hypotension. This can happen when your blood pressure lowers rapidly after you stand up from a lying down position.
The most common side effects of CYCLOSET include:
• nausea
• headache
• fatigue (somnolence). If you have somnolence from CYCLOSET you should not drive or use other heavy machines until the somnolence is better.
• dizziness
• vomiting
• low blood sugar (hypoglycemia), especially when used with another type of diabetes medicine known as a sulfonylurea

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of CYCLOSET. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CYCLOSET?
Store and dispense: At 68-77°F (20-25°C) in a tight, light-resistant container. See USP Controlled Room Temperature.

Keep CYCLOSET and all medicines out of the reach of children.

General information about the use of CYCLOSET
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use CYCLOSET for a condition for which it was not prescribed. Do not give CYCLOSET to other people, even if they have the same symptoms you have. It may harm them.