**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use PARLODEL safely and effectively. See full prescribing information for PARLODEL.**

**PARLODEL (bromocriptine mesylate) tablets, for oral use**
**PARLODEL (bromocriptine mesylate) capsules, for oral use**
**Initial U.S. Approval: 1978**

**----------RECENT MAJOR CHANGES----------**
- Dosage and Administration, recommended evaluation before initiating PARLODEL (2.1) ---------- 6/2026
- Dosage and Administration, dosage modification for strong and moderate CYP3A4 inhibitors (2.7) ---------- 6/2026
- Contraindications, history of cardiac valvular disorders; pericardial fibrosis; pleural, pulmonary, or retroperitoneal fibrotic disorders (4, 5.1, 5.2) ---------- 6/2026
- Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.8, 5.9) ---------- 6/2026

**----------INDICATIONS AND USAGE----------**
PARLODEL is an ergot derivative indicated for the treatment of:

- Hyperprolactinemia-associated dysfunction including amenorrhea with or without galactorrhea, infertility, or hypogonadism in adults (1.1)
- Prolactin-secreting adenomas in adults and pediatric patients 11 years of age and older (1.2).
- Acromegaly in adults (1.3).
- Signs and symptoms of idiopathic Parkinson's disease or postencephalitic parkinsonism in adults (1.4).

Limitations of Use
Avoid use of PARLODEL for the inhibition or suppression of postpartum physiologic lactation because of the risk of serious adverse reactions (1.1, 5.4)

**----------DOSAGE AND ADMINISTRATION----------**
- Before initiating PARLODEL, evaluate for valvular heart disease, including with an echocardiogram. If valvular disease is detected, do not administer PARLODEL (2.1).
- Take PARLODEL orally with food (2.2)
- Recommended dosage for hyperprolactinemia-associated dysfunction is 1.25 mg (one-half of a tablet) to 2.5 mg once daily. Increase the dosage up to 2.5 mg once daily every two to seven days within a recommended dosage of 2.5 mg to 15 mg once daily (2.3)
- Recommended dosage for prolactin-secreting adenomas is 1.25 mg to 2.5 mg once daily. Increase the dosage within a recommended dosage of 2.5 mg to 10 mg once daily (2.4)
- Recommended dosage for acromegaly is 1.25 to 2.5 mg once at bedtime for 3 days. Increase the dosage 1.25 mg to 2.5 mg once daily every 3 to 7 days up to the maximum recommended dosage is 100 mg/daily (2.5).
- Recommended starting dosage for idiopathic or postencephalitic Parkinson's disease is 1.25 mg twice daily. Increase the dosage by 1.25 mg twice daily every 14 to 28 days up to the maximum recommended daily dosage of 100 mg/day (2.6)
- For dosage modifications for concomitant use of PARLOEDL with moderate CYP3A4 inhibitors, see Full Prescribing Information (2.7, 7)

**----------DOSAGE FORMS AND STRENGTHS----------**
- Tablets: 2.5 mg of bromocriptine mesylate (functionally scored) (3)
- Capsules: 5 mg of bromocriptine mesylate (3)

**----------CONTRAINDICATIONS----------**
PARLODEL is contraindicated in patients with:

- History of cardiac valvular disorders or a history of pericardial fibrosis (4, 5.1).
- History of pleural, pulmonary, or retroperitoneal fibrotic disorders (4, 5.2)
- Uncontrolled hypertension (4, 5.3)
- Hypersensitivity to bromocriptine or to any of the excipients of PARLODEL or sensitivity to other ergot alkaloids (4).

**----------WARNINGS AND PRECAUTIONS----------**
- *Cardiac Valvulopathy and Pericardial Fibrosis:* During PARLODEL treatment, monitor for the development of valvulopathy with a cardiac echocardiogram at intervals of 6 to 12 months or as clinically indicated and monitor for chest pain and signs and symptoms of heart failure (if heart failure occurs, exclude valvular fibrosis and pericarditis). Consider additional clinical and diagnostic monitoring at baseline and as necessary during PARLODEL treatment. Use PARLODEL in patients treated with other drugs associated with valvulopathy is not recommended. Discontinue PARLODEL if the patient has a new diagnosis of valvular regurgitation, valvular restriction, valve leaflet thickening, or pericarditis. (5.1)
- *Pleural, Pulmonary and Retroperitoneal Fibrosis:* During PARLODEL treatment monitor for signs and symptoms of progressive fibrosis, (e.g., pleuro-pulmonary disease, renal impairment, ureteral/abdominal vascular obstruction). Consider clinical and diagnostic monitoring for pleural, pulmonary, and retroperitoneal fibrosis at baseline and as necessary during PARLODEL treatment. If pleural, pericardial, retroperitoneal, or pulmonary fibrosis occur, discontinue PARLODEL (5.2)
- *Hypotension/Orthostatic Hypotension:* Check blood pressure at baseline and during treatment with PARLODEL and monitor for hypotension. Patients with Parkinson's disease being treated with PARLODEL should be monitored for signs and symptoms of orthostatic hypotension (5.3)
- *Risks with Use of PARLODEL for Postpartum Lactation Inhibition or Suppression:* Avoid use of PARLODEL for the inhibition or suppression of physiologic lactation. Use of bromocriptine, another dopamine agonist for this unapproved use has been associated with cases of hypertension, stroke, myocardial infarction, seizures, and death. (5.4)
- *Impulse Control Disorders and Compulsive Behaviors:* Specifically ask patients about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating or other urges while being treated with PARLODEL. Consider dosage reduction or stopping PARLODEL if a patient develops such urges while taking PARLODEL. (5.5)
- *Falling Asleep During Activities of Daily Living:* If symptoms of daytime sleepiness or episodes of falling asleep occur while taking PARLODEL, advise patients not to drive or perform dangerous activities. Consider reducing the dosage or stopping PARLODEL if patients experience somulence or sudden sleep onset (5.6).
- *Visual Impariment in Patients with Prolactin-Secreting Adenomas:* Recommend monitoring of visual fields in PARLODEL-treated patients with macroprolactinoma for an early recognition of secondary field loss due to chiasmal herniation. PARLODEL-patients with rapidly progressive visual field loss should be evaluated by a neurosurgeon to help decide on the most appropriate therapy (5.7)
- *Exacerbation of Psychosis in Patients with Severe Psychotic Disorders:* Use of PARLODEL in patients with severe psychotic disorders in not recommended (5.8)

**----------ADVERSE REACTIONS----------**
Most common adverse reactions: (6.1)
- *Hyperprolactinemia-Associated Dysfunctions and Prolactin-secreting Adenomas:* (incidence >5%) are nausea, headache, dizziness, fatigue, lightheadedness, and vomiting.
- *Acromegaly:* (incidence >5%) are nausea, constipation, and postural/orthostatic hypotension.
- *Idiopathic Parkinson's Disease or Postencephalitic Parkinsonism:* nausea, abnormal involuntary movements, hallucinations, confusion

**To report SUSPECTED ADVERSE REACTIONS, contact Esjay Pharma LLC at 1-800-239-9339 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**----------DRUG INTERACTIONS----------**
- *Alcohol:* Alcohol may potentiate PARLODEL adverse reactions (7).
- *Dopamine Antagonists:* Concomitant use of PARLODEL with dopamine antagonists: decreased efficacy of PARLODEL (7).
- *Strong and Moderate CYP3A4 Inhibitors:* Avoid concomitant use of PARLODEL with strong CYP3A4 inhibitors. Dosage modifications are recommended for PARLODEL when used with a concomitant moderate CYP3A4 inhibitor (7).
- *Ergot Alkaloids:* Concomitant use of PARLODEL with other ergot alkaloids is not recommended. If use is unavoidable, dosage reduction may be needed where high PARLODEL dosages are used (7).

**----------USE IN SPECIFIC POPULATIONS----------**
- *Pregnancy:* See the Full Prescribing Information regarding the recommendations for using PARLODEL during pregnancy (8.1)

- *Lactation:* Avoid the use of PARLODEL during lactation in postpartum females.(8.2).
- *Females of Reproductive Potential:* A pregnancy test is recommended in PARLODEL-treated patients at least every 4 weeks during the amenorrheic period. Advise females of reproductive potential not seeking pregnancy, or those harboring large adenomas, to use appropriate contraceptive measures during PARLODEL treatment (8.3).

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 6/2026**

**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

### 1.1 Hyperprolactinemia-Associated Dysfunction
PARLODEL is indicated for the treatment of hyperprolactinemia-associated dysfunction including amenorrhea with or without galactorrhea, infertility or hypogonadism in adults.

Limitations of Use
Avoid use of PARLODEL for the inhibition or suppression of postpartum physiologic lactation because of the risk of serious adverse reactions *[see Warnings and Precautions (5.4)].*

### 1.2 Prolactin-Secreting Adenomas
PARLODEL is indicated for the treatment of prolactin-secreting adenomas in adults and pediatric patients 11 years of age and older.

### 1.3 Acromegaly
PARLODEL is indicated for the treatment of acromegaly in adults.

### 1.4 Idiopathic Parkinson's Disease or Postencephalitic Parkinsonism
PARLODEL is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease or postencephalitic parkinsonism in adults.

## 2 DOSAGE AND ADMINISTRATION
### 2.1 Recommended Evaluation Before Initiating PARLODEL
Before initiating PARLODEL evaluate for valvular heart disease, including with an echocardiogram. If valvular disease is detected, do not administer PARLODEL *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

### 2.2 Important Administration Instructions
Take PARLODEL orally with food because a high percentage of patients vomited after they received PARLODEL under fasting conditions.

### 2.3 Recommended Dosage for Hyperprolactinemia-Associated Dysfunction
The recommended starting dosage of PARLODEL in adults with hyperprolactinemia-associated dysfunction is 1.25 mg (one-half of a tablet) to 2.5 mg once daily. Increase the PARLODEL dosage up to 2.5 mg once daily every two to seven days as tolerated until an optimal therapeutic response is achieved within a recommended dosage of 2.5 mg to 15 mg once daily.

### 2.4 Recommended Dosage for Prolactin-Secreting Adenomas
The recommended starting dosage of PAROLDEL in adult and pediatric patients 11 years of age and older with prolactin-secreting adenomas is 1.25 mg (one-half of a tablet) to 2.5 mg once daily. Increase the PARLODEL dosage as tolerated until an optimal therapeutic response is achieved within a recommended dosage of 2.5 mg to 10 mg once daily.

In cases where adenectomy is elected for prolactin-secreting adenomas, a course of PARLODEL therapy may be used to reduce the tumor mass prior to surgery.

### 2.5 Recommended Dosage for Acromegaly

The recommended starting dosage of PARLODEL in adults for acromegaly is 1.25 mg (one-half of a tablet) to 2.5 mg once at bedtime for 3 days. Increase the dosage 1.25 mg to 2.5 mg once daily every 3 to 7 days, as tolerated, until an optimal therapeutic response is achieved. Reevaluate patients monthly and modify the dosage based on growth hormone levels and clinical response.
For adults with acromegaly, the usual optimal therapeutic dosage range varies from 20-30 mg once at bedtime in most patients, and the maximum recommended dosage is 100 mg/daily.

After a brief trial with PARLODEL therapy in adults with acromegaly, if there is no significant reduction in growth hormone levels and no changes in the clinical features of acromegaly consider increasing the dosage or discontinuing PARLODEL.

For patients with acromegaly treated with pituitary irradiation, withdraw PARLODEL (e.g., for four to eight weeks) on a yearly basis to assess the clinical effects of radiation on the disease process as well as the effects of PARLODEL therapy. Consider restarting PARLODEL if signs or symptoms of acromegaly or increases in growth hormone occur.

### 2.6 Recommended Dosage for Idiopathic Parkinson's Disease or Postencephalitic Parkinson Parkinsonism

The recommended starting dosage of PARLODEL in adults with idiopathic Parkinson's disease or postencephalitic parkinsonism is 1.25 mg (one-half of a tablet) twice daily. Increase the dosage by 1.25 mg (one half of a tablet) twice daily every 14 to 28 days based on therapeutic response and tolerability, up to the maximum recommended daily dosage of 100 mg/day.

For patients receiving concomitant levodopa, maintain the levodopa dosage during PARLODEL dosage escalation. If the levodopa dosage is decreased, increase the PARLODEL dosage in increments of 1.25 mg twice daily.

### 2.7 Dosage Modification for Strong and Moderate CYP3A4 Inhibitors

Avoid concomitant use of PARLODEL with strong CYP3A4 inhibitors. Dosage modifications of PARLODEL for concomitant use with moderate CYP3A4 inhibitors are provided in Table 1 *[see Drug Interactions (7)].*

**Table 1. Dosage Modifications of PARLODEL for Concomitant Use with Moderate CYP3A4 Inhibitors**

| | Starting Dosage | Maximum Dosage |
|---|---|---|
| Hyperprolactinemia-associated dysfunction in adults | 1.25 mg once daily (one-half of a tablet) | 3.75 mg once daily |
| Prolactin-secreting adenomas in adult and pediatric patients 11 years of age and older | 1.25 mg once daily | 2.5 mg once daily |
| Acromegaly in adults | 1.25 mg once daily | 25 mg once daily |
| Idiopathic or postencephalitic parkinsonism in adults | 1.25 mg once daily | 12.5 mg twice daily |

## 3 DOSAGE FORMS AND STRENGTHS

Tablets (SnapTabs®): 2.5 mg of bromocriptine, off-white, round, flat-faced, beveled-edge tablets, debossed “E” above the score and “280” below the score on one side and debossed “2.5” on the other side.

Capsules: 5 mg of bromocriptine , are caramel opaque cap imprinted “102” on the cap and white opaque body, imprinted with “PARLODEL” over “5 mg” on the body.

## 4 CONTRAINDICATIONS

PARLODEL is contraindicated in patients with:

- History of cardiac valvular disorders or a history of pericardial fibrosis *[see Warnings and Precautions (5.1)].*
- History of pleural, pulmonary, or retroperitoneal fibrotic disorders *[see Warnings and Precautions (5.2)].*
- Uncontrolled hypertension *[see Warnings and Precautions (5.3)].*
- Hypersensitivity to bromocriptine or to any of the excipients of PARLODEL or sensitivity to other ergot alkaloids.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cardiac Valvulopathy and Pericardial Fibrosis

Before initiating PARLODEL, perform a cardiovascular evaluation, including with an echocardiogram, to evaluate for valvular disease. PARLODEL is contraindicated in the presence of valvular disease or pericardial fibrosis. PARLODEL is not recommended in patients treated with other drugs associated with valvulopathy. Following PARLODEL treatment initiation, monitor for the development of valvulopathy with a cardiac echocardiogram at intervals of 6 to 12 months or as clinically indicated with new onset edema, cardiac murmur, dyspnea, or heart failure. During PARLODEL treatment, monitor for chest pain and signs and symptoms of heart failure and if heart failure occurs, valvular fibrosis and pericarditis should be excluded. Consider clinical and diagnostic monitoring such as erythrocyte sedimentation rate, serum creatinine measurements, chest-x-ray, and other investigations and cardiac imaging at baseline and as necessary while patients are treated with during PARLODEL treatment. Discontinue PARLODEL if the patient has a new diagnosis of valvular regurgitation, valvular restriction, valve leaflet thickening, or pericarditis.

Cases of cardiac valvulopathy have occurred in PARLODEL-treated patients. Pericardial effusions, as well as constrictive pericarditis, have been reported in PARLODEL-treated patients, particularly those on long-term and high-dosage treatment.

### 5.2 Pleural, Pulmonary, and Retroperitoneal Fibrosis

PARLODEL is contraindicated in patients with a history of pleural, pulmonary, or retroperitoneal fibrosis. During PARLODEL treatment monitor for signs and symptoms of progressive fibrosis, including:

- Pleuro-pulmonary disease (e.g., dyspnea, shortness of breath, persistent cough, chest pain).
- Renal impairment or ureteral/abdominal vascular obstruction (e.g., pain in the loin/flank, lower limb edema, abdominal masses or tenderness that may indicate retroperitoneal fibrosis).

Consider clinical and diagnostic monitoring for pleural, pulmonary, and retroperitoneal fibrosis such as with erythrocyte sedimentation rate, serum creatinine measurements, chest-x-ray, and other

investigations at baseline and as necessary during PARLODEL treatment. If pleural, pericardial, retroperitoneal, or pulmonary fibrosis occur, discontinue PARLODEL.

Pleural and Pulmonary Fibrosis
Patients with unexplained pleuropulmonary disorders should be examined thoroughly and discontinuation of PARLODEL therapy should be considered.

Pleural effusions, pleural fibrosis, and pulmonary fibrosis have been reported in PARLODEL-treated patients, particularly those on long-term and high-dosage treatment. In those instances in which PARLODEL treatment was stopped, the changes slowly reverted towards normal.

Retroperitoneal Fibrosis
To ensure recognition of retroperitoneal fibrosis at an early reversible stage recommend that patients on long-term and high-dosage treatment should be monitored for its manifestations (e.g., back pain, lower limb edema, impaired kidney function). PARLODEL should be withdrawn if fibrotic changes in the retroperitoneum are diagnosed or suspected.

Retroperitoneal fibrosis has been reported in a few PARLODEL-treated patients, particularly those on long-term and high-dosage treatment. Retroperitoneal fibrosis has been reported in a few patients with Parkinson's disease who received long-term PARLODEL therapy (2 to 10 years) in dosages that ranged from 30 mg daily to 140 mg daily (9.3, 1.4, and 1.4 times the maximum recommended PARLODEL dosage for the hyperprolactionemia-associate dysfunction, acromegaly, and idiopathic Parkinson's disease or postencephalitic parkinsonism indications, respectively *[see Dosage and Administration (2.6)]).*

**5.3 Hypotension/Orthostatic Hypotension**
Hypotension/Orthostatic Hypotension
Check blood pressure at baseline and during treatment with PARLODEL and monitor for hypotension. Instruct patients to report dizziness or lightheadedness with changes in position to their healthcare provider. Particular care should be exercised in PARLODEL-treated patients when driving a vehicle or operating hazardous machinery.

Hypotensive reactions may occur during PARLODEL treatment, especially during the first days of treatment.

Orthostatic Hypotension in Patients with Parkinson's Disease
Patients with Parkinson's disease being treated with dopaminergic agonists, including PARLODEL, should be monitored for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk because patients with Parkinson's disease may have an impaired capacity to respond to an orthostatic challenge.

**5.4 Risks with Use of PARLODEL for Postpartum Lactation Inhibition or Suppression**
Avoid use of PARLODEL for the inhibition or suppression of postpartum physiologic lactation. Use of PARLODEL for this unapproved use has been associated with serious adverse reactions, including hypertension, psychotic reactions, acute myocardial infarction, seizures (including status epilepticus), stroke, and death.

- Hypertension has occurred at the initiation of PARLODEL therapy, but often in the second week of therapy.

- Seizures have been reported with and without the prior development of hypertension.
- Stroke has mostly occurred in postpartum females whose prenatal and obstetric courses had been uncomplicated.

Many of the PARLODEL-treated patients who experienced seizures (including cases of status epilepticus) and/or strokes reported developing a constant and often progressively severe headache accompanied by visual disturbance hours to days prior to the acute event. Some cases of strokes and seizures were also preceded by visual disturbances (blurred vision, and transient cortical blindness).

In postmarketing experience in the U.S., serious adverse reactions reported in PARLODEL-treated postpartum patients included 72 cases of seizures (including 4 cases of status epilepticus), 30 cases of stroke, and 9 cases of myocardial infarction. One stroke case was associated with sagittal sinus thrombosis, and another was associated with cerebral and cerebellar vasculitis. One case of myocardial infarction was associated with unexplained disseminated intravascular coagulation and a second occurred in conjunction with use of another ergot alkaloid.

**5.5 Impulse Control Disorders and Compulsive Behaviors**
Because patients may not recognize impulse control and compulsive behaviors as abnormal, it is important for healthcare providers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with PARLODEL. Consider dosage reduction or stopping PARLODEL if a patient develops such urges while taking PARLODEL.

Patients can experience intense urges to gamble or to spend money, increased sexual urges, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more drugs that increase central dopaminergic tone, including PARLODEL. In some cases, these urges were reported to have stopped when the dosage was reduced, or the drug was discontinued.

**5.6 Falling Asleep During Activities of Daily Living**
Before initiating treatment with PARLODEL, advise patients of the potential to develop drowsiness and specifically ask them about factors that may increase their risk for somnolence with dopaminergic drugs, such as concomitant sedating drugs or the presence of a sleep disorder. If a patient develops daytime sleepiness or episodes of falling asleep during activities that require full attention (e.g., driving a motor vehicle, conversations, eating), consider reducing the PARLODEL dosage or discontinuing PARLODEL. If a decision is made to continue PARLODEL, advise the patient to avoid driving or performing potentially dangerous activities.

Patients treated with dopaminergic drugs, including PARLODEL, have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes has resulted in accidents. Patients may not perceive warning signs, such as excessive drowsiness, or they may report feeling alert immediately prior to the event.

**5.7 Visual Impairment in Patients with Prolactin-secreting Adenomas**
Recommend monitoring of visual fields in PARLODEL-treated patients with macroprolactinoma for an early recognition of secondary field loss due to chiasmal herniation. PARLODEL-patients with rapidly progressive visual field loss should be evaluated by a neurosurgeon to help decide on the most appropriate therapy.

In some PARLODEL-patients patients, a secondary deterioration of visual fields may develop (despite normalized prolactin levels and tumor shrinkage) which may result from traction on the optic chiasm which is pulled down into the now partially empty sella. Reduction of the PARLODEL dosage may improve the visual field defect (there may be some elevation of prolactin and tumor re-expansion). The relative efficacy of PARLODEL versus surgery in preserving visual fields in patients with prolactin-secreting adenomas is not known.

**5.8 Exacerbation of Psychosis in Patients with Severe Psychotic Disorders**
The use of PARLODEL in patients with severe psychotic disorders is not recommended.

In patients with severe psychotic disorders, treatment with a dopamine receptor agonist including PARLODEL may exacerbate the psychosis or may diminish the effectiveness of drugs used to treat the severe psychotic disorder.

**5.9 Risks in Patients with Hereditary Problems of Galactose Intolerance, Severe Lactase Deficiency, or Glucose-Galactose Malabsorption**
Avoid use of PARLODEL in patients with rare hereditary problems of galactose intolerance, severe lactase deficiency, or glucose-galactose malabsorption. PARLODEL contains lactose as an inactive ingredient.

The use of lactose in patients with rare hereditary problems of galactose intolerance, severe lactase deficiency, or glucose-galactose malabsorption increases the risk of diarrhea, abdominal pain, bloating, and malabsorption.

**5.10 Additional Clinically Significant Adverse Reactions and Risks in Patients with Acromegaly**
Cold-sensitive Digital Vasospasm
Vasospam may be prevented in PARLODEL-treated patients by keeping the fingers warm.

Cold-sensitive digital vasospasm has been observed in some PARLODEL-treated patients with acromegly. If vasospasm occurs, it can be reversed by reducing the PARLODEL dosage.

Gastrointestinal Bleeding
Patients with a history of peptic ulcer or gastrointestinal bleeding should be monitored carefully during PARLODEL treatment.

Cases of severe gastrointestinal bleeding from peptic ulcers have been reported, some fatal, in PARLODEL-treated patients.

Tumor Expansion
Because the natural history of growth hormone-secreting tumors is unknown, PARLODEL-treated patients with acromegaly should be carefully monitored and, if evidence of tumor expansion develops, discontinuation of PARLODEL treatment and alternative procedures should be considered.

Possible growth hormone-secreting tumor expansion has been reported in a few PARLODEL-treated patients.

Withdrawal Adverse Reactions After Rapid Dosage Reduction or Discontinuation
Prior to PARLODEL discontinuation, patients with acromegaly should be informed about a potential withdrawal symptom, and closely monitored during and after PARLODEL discontinuation. PARLODEL discontinuation should be undertaken gradually whenever possible. In case of severe withdrawal symptoms, consider re-administration of PARLODEL in patients with acromegaly at the lowest effective dosage.

### 5.11 Additional Clinically Significant Adverse Reactions and Risks in Patients with Idiopathic Parkinson's Disease or Postencephalitic Parkinsonism

Mental Disturbances and Psychotic Symptoms
PARLODEL administered alone or concomitantly with levodopa may cause hallucinations (visual or auditory). Hallucinations may be accompanied by abnormal thinking and behavior which may present with one or more symptoms, including paranoid ideation, delusions, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium. Symptoms may be more frequent at higher dosages. Because of the risk of exacerbation of mental disturbances in patients with Parkison's disease-related dementia, consider a lower PARLODEL dosage in these patients. The use of PARLODEL in patients with severe psychotic disorders is not recommended *[see Warnings and Precautions (5.8)].*

Hallucinations usually resolve with PARLODEL dosage reduction; occasionally, discontinuation of PARLODEL is required. Rarely, after high PARLODEL dosage treatment, hallucinations have persisted for several weeks following PARLODEL discontinuation .

Risk of Exacerbation of Arrhythmias in Patients with a History of Myocardial Infarction with a Residual Arrthythmia
Caution should be exercised when administering PARLODEL to patients with a history of myocardial infarction who have a residual atrial, nodal, or ventricular arrhythmia.

Withdrawal Adverse Reactions After Rapid Dosage Reduction or Discontinuation
Prior to PARLODEL discontinuation, patients should be informed about potential withdrawal symptoms, and closely monitored during and after PARLODEL discontinuation. PARLODEL discontinuation should be undertaken gradually whenever possible, even if the patient is to remain on levodopa. In case of severe withdrawal symptoms, consider re-administration of PARLODEL at the lowest effective dosage.

A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dosage reduction or withdrawal of antiparkinsonian therapy. Symptoms including apathy, anxiety, depression, fatigue, insomnia, sweating, and pain have been reported during taper or after discontinuation of dopamine agonists, including PARLODEL. These withdrawal symptoms generally have not responded to levodopa.

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cardiac Valvulopathy and Pericardial Fibrosis *[see Warnings and Precautions (5.1)]*
- Pleural, Pulmonary, and Retroperitoneal Fibrosis *[see Warnings and Precautions (5.2)]*

- Hypotension/Orthostatic Hypotension *[see Warnings and Precautions (5.3)]*
- Risks with Use of PARLODEL for Postpartum Lactation Inhibition or Suppression *[see Warnings and Precautions (5.4)]*
- Impulse Control Disorders and Compulsive Behaviors *[see Warnings and Precautions (5.5)]*
- Falling Asleep During Activities of Daily Living *[see Warnings and Precautions (5.6)]*
- Visual Impairment in Patients with Prolactin-secreting Adenomas *[see Warnings and Precautions (5.7)]*
- Exacerbation of Psychosis in Patients with Severe Psychotic Disorders *[see Warnings and Precautions (5.8)]*
- Risks in Patients with Hereditary Problems of Galactose Intolerance, Severe Lactase Deficiency, or Glucose-Galactose Malabsorption *[see Warnings and Precautions (5.9)]*
- Additional Clinically Significant Adverse Reactions and Risks in Patients with Acromegaly *[see Warnings and Precautions (5.10)]*
- Additional Clinically Significant Adverse Reactions and Risks in Patients with Idiopathic Parkinson's Disease or Postencephalitic Parkinsonism *[see Warnings and Precautions (5.11)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Studies of Patients with Hyperprolactinemia-Associated Dysfunctions and Prolactin-secreting Adenomas

PARLODEL therapy was discontinued in approximately 5% of patients with hyperprolactinemia-associated dysfunctions. The most common adverse reactions in PARLODEL-treated patients with hyperprolactinemia-associated dysfunctions were nausea (49%), headache (19%), dizziness (17%), fatigue (7%), lightheadedness (5%), vomiting (5%), abdominal cramps (4%), nasal congestion (3%), constipation (3%), diarrhea (3%) and drowsiness (3%).

A few cases of cerebrospinal fluid rhinorrhea have been reported in PARLODEL-treated patients with large prolactinomas who have received previous transsphenoidal surgery, pituitary radiation, or both.

Adverse Reactions in Studies of Patients with Acromegaly

The most frequent adverse reactions in PARLODEL-treated patients with acromegaly were nausea (18%), constipation (14%), postural/orthostatic hypotension (6%), anorexia (4%), dry mouth/nasal stuffiness (4%), indigestion/dyspepsia (4%), digital vasospasm (3%), drowsiness/tiredness (3%) and vomiting (2%).

Adverse reactions that occurred in less than 2% of PARLODEL-treated patients with acromegaly were gastrointestinal bleeding, dizziness, exacerbation of Raynaud's syndrome, headache, and syncope.

Adverse reactions that occured in less than 1% of PARLODEL-treated patients with acromegaly were hair loss, alcohol potentiation, faintness, lightheadedness, arrhythmia, ventricular tachycardia, decreased sleep requirement, visual hallucinations, lassitude, shortness of breath, bradycardia, vertigo, paresthesia, sluggishness, vasovagal attack, delusional psychosis, paranoia, insomnia, heavy headedness, reduced tolerance to cold, tingling of ears, facial pallor, and muscle cramps.

Adverse Reactions in Studies of Patients with Idiopathic Parkinson's Disease or Postencephalitic Parkinsonism

In clinical trials in PARLODEL-treated patients with idiopathic Parkinson's disease or postencephalitic parkinsonism where patients had a reduction in the levodopa/carbidopa dosage, the most common adverse reactions were nausea, abnormal involuntary movements, hallucinations, confusion, "on-off'' phenomenon, dizziness, drowsiness, faintness/fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation, and vertigo.

Less common adverse reactions in PARLODEL-treated patients with idiopathic Parkinson's disease or postencephalitic parkinsonismwere anorexia, anxiety, blepharospasm, dry mouth, dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizure, fatigue, headache, lethargy, mottling of skin, nasal stuffiness, nervousness, nightmares, paresthesia, skin rash, urinary frequency, urinary incontinence, urinary retention, and rarely, signs and symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's syndrome.

Abnormalities in laboratory tests in PARLODEL-treated patients with idiopathic or postencephalitic Parkinson's disease may include elevations in blood urea nitrogen, ALT, AST, GGPT, CPK, alkaline phosphatase and uric acid, which are usually transient.

Additional Adverse Reactions in Clinical Studies of PARLODEL

During clinical trials, dizziness, drowsiness, faintness, fainting, and syncope have been reported early in the course of PARLODEL therapy.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of PARLODEL. 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.

- *Cardiac disorders:* Pericardial effusion, constrictive pericarditis, tachycardia, bradycardia, arrhythmia, cardiac valve fibrosis.
- *Ear and labyrinth disorders:* Tinnitus.
- *Eye disorders:* Visual disturbance, vision blurred.
- *General disorders and administration site conditions:* Fatigue, peripheral edema.
- *Gastrointestinal disorders:* Nausea, constipation, vomiting, dry mouth, diarrhea, abdominal pain, retroperitoneal fibrosis, gastrointestinal ulcer, gastrointestinal hemorrhage.
- *Musculoskeletal and connective tissue disorders:* Leg cramps.
- *Nervous system disorders:* Headache, drowsiness, dizziness, dyskinesia, somnolence, paraesthesia, excess daytime somnolence, sudden onset of sleep.
- *Respiratory, thoracic and mediastinal disorders:* Nasal congestion, pleural effusion, pleural fibrosis, pleurisy, pulmonary fibrosis, dyspnea.
- *Psychiatric disorders:* Confusion, psychomotor agitation/excitation, hallucinations, psychotic disorders, insomnia, libido increase, hypersexuality, and impulse control/compulsive behaviors (including gambling, spending, and other intense urges).
- *Skin and subcutaneous tissue disorders:* Allergic skin reactions, hair loss.
- *Vascular disorders:* Hypotension, orthostatic hypotension (very rarely leading to syncope), reversible pallor of fingers and toes induced by cold (especially in patients with history of Raynaud's phenomenon).

## 7 DRUG INTERACTIONS

Alcohol

Alcohol may potentiate PARLODEL-associated adverse reactions.

Dopamine Antagonists

The concomitant use of PARLODEL with dopamine antagonists resulted in a decreased efficacy of PARLODEL.

Strong and Moderate CYP3A4 Inhibitors

Avoid concomitant use of PARLODEL with strong CYP3A4 inhibitors. Follow the recommended PARLODEL dosage modifications during concomitant use with moderate CYP3A4 inhibitors *[see Dosage and Administration (2.7)].*

Bromocriptine is a substrate of CYP3A4 *[see Clinical Pharmacology (12.3)]*. Concomitant use with strong and moderate CYP3A4 inhibitors increases bromocriptine exposure *[see Clinical Pharmacology (12.3)],* which may increase the risk of PARLODEL-associated adverse reactions.

Ergot Alkaloids

Concomitant use of PARLODEL with other ergot alkaloids is not recommended. If use is unavoidable, dosage reduction may be necessary in those cases where high dosages of PARLODEL are being used (such as patients with Parkinson's disease).

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

*Pregnancy in Patients with Hyperprolactinemia-Associated Dysfunction and Prolactin-Secreting Adenomas:* In patients being treated with PARLODEL for hyperprolactinemia, PARLODEL should generally be withdrawn when pregnancy is diagnosed. If PARLODEL is continued or reinstituted in select patients to manage a prolactin-secreting macroadenoma and a patient experiences a hypertensive disorder of pregnancy, the benefit of continuing PARLODEL should be weighed against the possible risk of its use during a hypertensive disorder of pregnancy.

*Pregnancy in Patients with Acromegaly*: In patients being treated with PARLODEL for acromegaly who subsequently become pregnant, a decision should be made as to whether PARLODEL continues to be medically necessary or can be withdrawn. PARLODEL should be withdrawn in those who experience hypertensive disorders of pregnancy (including eclampsia, preeclampsia, or pregnancy-induced hypertension) unless PARLODEL use is necessary.

*Idiopathic Parkinson's Disease or Postencephalitic Parkinsonism:* In patients being treated with PARLODEL for idiopathic Parkinson's disease or postencephalitic parkinsonism, there are no adequate data on the developmental risk associated with the use of the PARLODEL in pregnant women. If the decision is made to discontinue PARLODEL, adverse reactions associated with rapid dosage reduction or withdrawal should be considered *[see Warnings and Precatutions (5.11)].*

*Risk of Major Birth Defects and Miscarriage:* The estimated background risk of major birth defects and miscarriage in patients with hyperprolactinemia-associated dysfunctions, prolactin-secreting ademonas, acromegaly, or idiopathic Parkinson's disease or postencephalitic parkinsonism is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S.

general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The incidence of birth defects in 1,109 live births was 3.3% in neonates/infants born to mothers who received PARLODEL during pregnancy *(see Data)*.

Clinical Considerations

*Maternal Adverse Reactions:* PARLODEL-treated patients should be monitored closely throughout pregnancy for signs and symptoms that may signal the enlargement of a previously undetected or existing prolactin-secreting tumor. Discontinuation of PARLODEL treatment in patients with known macroadenomas has been associated with rapid regrowth of tumor and increase in serum prolactin in most cases.

Prolactin-secreting adenomas may expand and compression of the optic or other cranial nerves may occur, emergency pituitary surgery becoming necessary. In most cases, the compression resolves following delivery. Reinitiation of PARLODEL treatment has been reported to produce improvement in the visual fields of patients in whom nerve compression has occurred during pregnancy.

*Postpartum Period:* Avoid use of PARLODEL for the inhibition or suppression of postpartum physiologic lactation because of the risk of serious adverse reactions *[see Warnings and Precautions (5.4)]*.

PARLODEL should not be used during the postpartum period in women with a history of coronary artery disease and other severe cardiovascular conditions unless PARLODEL use is necessary.

Symptomatic hypotension can occur in PARLODEL-treated patients. In postpartum studies, decreases in supine systolic blood pressure (SBP) and diastolic blood pressure of greater than 20 mm and 10 mm Hg, respectively, were observed in almost 30% of PARLODEL-treated patients. On occasion, the drop in supine SBP was as much as 50-59 mm of Hg.

Data

*Human Data*: The following information is based on 1,276 pregnancies in PARLODEL-treated females. In the majority of cases, PARLODEL was discontinued within 8 weeks into pregnancy (mean 29 days), however, eight patients received the PARLODEL continuously throughout pregnancy. The mean PARLODEL dosage for pregnant patients was 6 mg (range 1-40 mg) per day.

Of these 1,276 pregnancies, there were 1,088 full-term deliveries (4 stillborn), 145 spontaneous abortions (11%), and 28 induced abortions (2%). Moreover, 12 extrauterinegravidities 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. There is no evidence that PARLODEL contributed to the type or incidence of birth defects in these infants.

*Animal Data:* Administration of 10-30 mg/kg of bromocriptine to rats (two strains) on days 6 to 15 postcoitum as well as a single bromocriptine dose of 10 mg/kg on day 5 postcoitum interfered with implantation. Administration of 3 mg/kg of bromocriptine on days 6 to 15 were without effect on nidation, and did not produce any anomalies in the rats. Rats treated with 30 mg/kg of bromocriptine from day 8-15 postcoitum (i.e., after implantation) produced increased prenatal mortality with increased incidence of embryonic resorption. One anomaly, aplasia of spinal vertebrae and ribs, was

found in the group of 262 fetuses derived from the dams. No fetotoxic effects were found in offspring of dams treated with bromocriptine during the peri-or postnatal period.

Two studies were conducted in rabbits (two strains) to determine the potential of bromocriptine to interfere with nidation. Bromocriptine dose levels of 100 or 300 mg/kg/day from day 1 to day 6 postcoitum did not adversely affect nidation. The high dose was approximately 63 times the maximum human recommended dose administered in controlled clinical trials in patients with acromegaly (100 mg/day), based on body surface area. In New Zealand white rabbits, some embryo mortality occurred at a bromocriptine dose of 300 mg/kg which was a reflection of overt maternal toxicity. Three studies were conducted in two strains of rabbits to determine the teratological potential of bromocriptine at dose levels of 3, 10, 30, 100, and 300 mg/kg administered from day 6 to day 18 postcoitum. In two studies with the Yellow-silver strain, cleft palate was found in 3 and 2 fetuses at maternally toxic bromocriptine doses of 100 and 300 mg/kg, respectively. One control fetus also exhibited this anomaly. In the third study conducted with New Zealand white rabbits using an identical protocol, no cleft palates were observed.

No teratological or embryotoxic effects of bromocriptine were produced in any of six offspring from six monkeys at a bromocriptine dose level of 2 mg/kg.

### 8.2 Lactation

Risk Summary

Avoid the use of PARLODEL during lactation in postpartum females.

### 8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Because pregnancy may occur prior to reinitiation of menses, a pregnancy test is recommended in PARLODEL-treated patients at least every 4 weeks during the amenorrheic period or every time a patient misses a menstrual period in those who have menses. If menstruation does not occur within 3 days of the expected date, consider discontinuing PARLODEL and a pregnancy test should be performed.

Contraception

*Females*: Patients not seeking pregnancy, or those harboring large adenomas, should be advised to use appropriate contraceptive measures during treatment with PARLODEL.

### 8.4 Pediatric Use

The safety and effectiveness of PARLODEL have been established for the treatment of prolactin-secreting pituitary adenomas in pediatric patients 11 years of age and older. Use of PARLODEL for this indication is supported by evidence from adequate and well-controlled trials of PARLODEL in adults with hyerprolactinemia-associated dysfunction, with additional data in 14 PARLODEL-treated pediatric patients 11 to 15 years of age with prolactin-secreting pituitary macro-and microadenomas. Chronic hypopituitarism complicated macroadenoma treatment in 5 of the responders, in patients treated with PARLODEL alone and in those treated with PARLODEL in combination with surgical treatment and/or pituitary irradiation.

The safety and effectiveness of PARLODEL have not been established for the treatment of prolactin-secreting adenomas in pediatric patients less than 11 years of age.

The safety and effectiveness of PARLODEL have not been established in pediatric patients for the treatment of hyperprolactiniemia-associated dysfunction, acromegaly, or idiopathic Parkinson's disease or postencephalitic parkinsonism.

### 8.5 Geriatric Use
Clinical studies of PARLODEL did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

## 9 DRUG ABUSE AND DEPENDENCE
### 9.1 Controlled Substance
PARLODEL contains bromocriptine, which is not a controlled substance.

### 9.3 Dependence
Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Apathy, anxiety, depression, fatigue, insomnia, sweating, and pain have been reported during taper or after discontinuation of dopamine agonists, including PARLODEL. A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability) has been reported in association with rapid dosage reduction or withdrawal of PARLODEL *[see Warnings and Precautions (5.11)].*

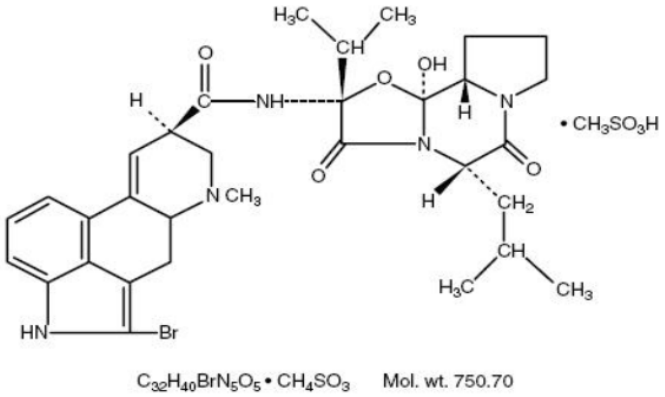
## 10 OVERDOSAGE
The most commonly reported signs and symptoms associated with acute PARLODEL overdose are nausea, vomiting, constipation, diaphoresis, dizziness, pallor, severe hypotension, malaise, confusion, lethargy, drowsiness, delusions, hallucinations, and repetitive yawning.

Overdose signs and symptoms from isolated reports of children who accidentally ingested PARLODEL included vomiting, somnolence and fever. The children recovered either spontaneously within a few hours or after appropriate management.

If an overdose occurs, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for overdose management recommendations.

## 11 DESCRIPTION
Bromocriptine mesylate is an ergot derivative with potent dopamine receptor agonist activity. Bromocriptine mesylate is chemically designated as Ergotaman-3′, 6′, 18-trione, 2-bromo-12′-hydroxy-2′- (1-methylethyl) -5′-(2-methylpropyl) -, (5′α) -monomethanesulfonate (salt).

The structural formula is:



$C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$ Mol. wt. 750.70

Complies with USP dissolution test 1.

PARLODEL (bromocriptine mesylate) tablets (SnapTabs) and PARLODEL (bromocriptine mesylate) capsules are for oral administration.

- *PARLODEL (bromocriptine mesylate) tablets:* Each tablet contains 2.5 mg of bromocriptine (equivalent to 2.87 mg of bromocriptine mesylate) and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate *[see Warnings and Precautions (5.9)],* magnesium stearate, maleic acid, povidone and corn starch.
- *PARLODEL (bromocriptine mesylate) capsules:* Each capsule contains 5 mg of bromocriptine (equivalent to 5.74 mg of bromocriptine mesylate) and the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate *[see Warnings and Precautions (5.9)]*, magnesium stearate, and maleic acid. The hard gelatin capsule contains gelatin, iron oxide red, titanium dioxide and purified water. The imprinting ink contains black iron oxide, butyl alcohol, dehydrated alcohol, isopropyl alcohol, propylene glycol and shellac.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

PARLODEL contains bromocriptine, an ergot derivative and dopamine receptor agonist, which activates post-synaptic dopamine receptors. Dopaminergic neurons in the tuberoinfundibular process release dopamine that modulates the secretion of prolactin from the anterior pituitary; in the corpus striatum the dopaminergic neurons are involved in the control of motor function.

Bromocriptine induces stereotyped behavior in rodents and turning behavior in rats (e.g., rats move in circles) that have unilateral lesions in the substantia nigra. These actions, characteristic of those produced by dopamine, are inhibited by dopamine antagonists and suggest a direct action of bromocriptine on striatal dopamine receptors.

Bromocriptine inhibits the secretion of prolactin in humans, with little or no effect on other pituitary hormones, except in patients with acromegaly, where bromocriptine lowers elevated blood levels of growth hormone in the majority of patients.

Bromocriptine produces its therapeutic effect in the treatment of idiopathic Parkinson’s disease or postencephalitic parkinsonism, a clinical condition characterized by a progressive deficiency in dopamine synthesis in the substantia nigra, by directly stimulating the dopamine receptors in the corpus striatum.

## 12.2 Pharmacodynamics

Clinically, PARLODEL significantly reduces plasma levels of prolactin in patients with hyperprolactinemia. The inhibition of physiological lactation as well as galactorrhea in pathological hyperprolactinemic states is obtained at dose levels that do not affect secretion of other tropic hormones from the anterior pituitary.

Cardiac Electrophysiology

There is insufficient information to characterize the effect of PARLODEL on the QTc interval.

## 12.3 Pharmacokinetics

Following single 5 mg PARLODEL dose (two 2.5 mg tablets) to five healthy volunteers under fasted conditions, the mean peak bromocriptine plasma levels, time to reach peak bromocriptine plasma concentrations and elimination half-life were 465 pg/mL ± 226, 2.5 hours ± 2 and 4.9 hours, respectively. Linear relationship was found between single doses of PARLODEL and Cmax and AUC in the dose range of 1 to 7.5 mg. The pharmacokinetics of bromocriptine metabolites is unknown.

Following administration of 5 mg of PARLODEL twice daily for 14 days, the bromocriptine Cmax and AUC at steady-state were 628 ± 375 pg/mL and 2377 ± 1186 pg*hr/mL, respectively.

Absorption

*Effect of Food:* Food did not significantly affect the systemic bromocriptine exposure following administration of 2.5 mg of PARLODEL.

Distribution

In vitro experiments showed that bromocriptine was 90% -96% bound to serum albumin.

Elimination

*Metabolism:* Bromocriptine undergoes extensive first-pass biotransformation, reflected by complex metabolite profiles and by almost complete absence of parent drug in urine and feces. In vitro studies using human liver microsomes showed that bromocriptine has a high affinity for CYP3A and hydroxylations at the proline ring of the cyclopeptide moiety constituted a main metabolic pathway. The participation of other major CYP enzymes such as 2D6, 2C8, and 2C19 in the metabolism of bromocriptine has not been evaluated.

*Excretion:* About 82% and 6% of the radioactive bromocriptine dose orally administered was recovered in feces and urine, respectively. Bromolysergic acid and bromoisolysergic acid accounted for half of the radioactivity in urine

Specific Populations

The effect of age, race, and sex on the pharmacokinetics of bromocriptine and its metabolites has not been evaluated.

*Patients with Renal Impairment:* The effect of renal function on the pharmacokinetics of bromocriptine has not been evaluated. Because parent drug and metabolites are almost completely excreted via metabolism, and only 6% eliminated via the kidney, renal impairment may not have a significant impact on the PK of bromocriptine and its metabolites.

*Patients with Hepatic Impairment:* The effect of hepatic impairment on the PK of bromocriptine and its metabolites has not been evaluated.

Drug Interaction Studies

Inhibitors and/or potent substrates for CYP3A4 might inhibit the clearance of bromocriptine and lead to increased bromocriptine levels *[see Drug Interactions (7)].* Bromocriptine is a CYP3A4 inhibitor with a calculated IC50 value of 1.69 μM.6 Given the low therapeutic bromocriptine concentrations in patients (Cmax=0.82 nM), a significant alteration of the metabolism of a second drug whose clearance is mediated by CYP3A4 is not be expected.

The potential effect of bromocriptine and its metabolites to act as CYP inducers has not been reported.

The concomitant use of erythromycin, a moderate CYP3A4 inhibitor, with PARLODEL was shown to increase the plasma levels of bromocriptine (mean AUC and Cmax values increased 3.7 fold and 4.6-fold, respectively) *[see Dosage and Administration (2.6) and Drug Interactions (7)].*.

The concomitant use of PARLODEL and octreotide in patients with acromegaly led to increased plasma bromocriptine levels (bromocriptine AUC increased about 38%) . These changes in bromocriptione levels are not clinically significant.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A 74-week study was conducted in mice using dietary levels of bromocriptine mesylate equivalent to oral doses of 10 and 50 mg/kg/day. A 100-week study in rats was conducted using dietary levels of bromocriptine mesylate equivalent to oral doses of 1.7, 9.8, and 44 mg/kg/day. The highest doses of bromocriptine mesylate tested in mice and rats were approximately 2.5 and 4.4 times, respectively, the maximum recommended human dose (MRHD) of PARLODEL administered in controlled clinical trials in patients with acromegaly (100 mg/day) based on body surface area.

Malignant uterine tumors, endometrial and myometrial, were found in rats as follows: 0/50 control females, 2/50 females given 1.7 mg/kg daily, 7/49 females given 9.8 mg/kg daily, and 9/50 females given 44 mg/kg daily. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio which occurs in rats as a result of the prolactin-inhibiting action of bromocriptine mesylate. The endocrine mechanisms believed to be involved in the rats are not present in humans. There is no known correlation between uterine malignancies that occurred in bromocriptine-treated rats and human risk. In contrast to the findings in rats, the uteri from mice killed after 74 weeks of treatment did not exhibit evidence of drug-related changes.

Mutagenesis

Bromocriptine mesylate was evaluated for mutagenic potential in the battery of tests that included Ames bacterial mutation assay, mutagenic activity in vitro on V79 Chinese hamster fibroblasts, cytogenetic analysis of Chinese hamster bone marrow cells following in vivo treatment, and an in vivo micronucleus test for mutagenic potential in mice. No mutagenic effects were observed in any of these tests.

Impairment of Fertility
Fertility and reproductive performance in female rats were not influenced adversely by bromocriptine treatment beyond the predicted decrease in pup weight due to lactation suppression. In males treated with 50 mg/kg of bromocriptine, mating and fertility were within the normal range. Increased perinatal loss was produced in the subgroups of dams, sacrificed on day 21 postpartum after mating with males treated with the highest bromocriptine dose (50mg/kg).

## 14 CLINICAL STUDIES

### 14.1 Clinical Studies in Patients with Hyperprolactinemia-Associated Dysfunctions and Prolactin-secreting Adenomas

In about 75% of cases of amenorrhea and galactorrhea, PARLODEL suppressed galactorrhea completely, or almost completely, and reinitiated normal ovulatory menstrual cycles. Menses were usually reinitiated prior to complete suppression of galactorrhea; the time for this on average was 6 to 8 weeks. However, some patients responded within a few days, and other patients responded in up to 8 months.

At least a 75% reduction in secretion was observed after 8 to 12 weeks; however, some patients failed to respond even after 12 months of PARLODEL therapy.

Reduction in tumor size of prolactin-secreting adenomas has been demonstrated in both PARLODEL-treated male and female patients with macroadenomas.

### 14.2 Clinical Studies in Patients with Acromegaly

PARLODEL therapy, alone or as adjunctive therapy with pituitary irradiation or surgery, reduced serum growth hormone by 50% or more in approximately 50% of patients with acromegaly, although not usually to normal levels. Because the effects of external pituitary radiation may not become maximal for several years, adjunctive therapy with PARLODEL offers potential benefit before the effects of irradiation are manifested.

Virtually all acromegalic patients who received therapeutic benefit from PARLODEL also had reductions in circulating levels of growth hormone.

### 14.3 Clinical Studies in Patients with Idiopathic Parkinson's Disease or Postencephalitic Parkinsonism

PARLODEL in combination with levodopa or in combination with levodopa and a peripheral decarboxylase inhibitor may provide additional therapeutic benefits in patients with idiopathic Parkinson's disease or postencephalitic parkinsonism who are maintained on therapeutic levodopa dosages, who develop levodopa tolerance, or experience "end of dose failure'' on levodopa therapy.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

PARLODEL (bromocriptine mesylate) tablets (SnapTabs)
Tablets contain 2.5 mg of bromocriptine and are off-white, round, flat-faced, beveled-edge tablets, debossed "E" above the score and "280" below the score on one side and debossed "2.5" on the other sider.

- Bottles of 30 …….NDC 70685-260-01
- Bottles of 100……NDC 70685-260-02

PARLODEL (bromocriptine mesylate) capsules
Capsules contain 5 mg of bromocriptine and are hard gelatin capsule size 3 with caramelopaque cap imprinted “102” on the cap and white opaque body, imprinted with “PARLODEL” over “5 mg” on the body.

- Packages of 30……..…NDC 70685-270-01
- Packages of 100……NDC 70685-270-02

Store and Dispense
Store at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature].

Protect from light. Dispense in a tight, light-resistant container.

## 17 PATIENT COUNSELING INFORMATION

Fibrotic Conditions
There is a risk of cardiac valvulopathy, and pericardial, pleural, pulmonary, and retroperitoneal fibrosis with PARLODEL treatment Advise patients to notify their healthcare provider if they develop shortness of breath, chest pain, persistent cough, difficulty with breathing when lying down, or swelling in their extremities *[see Warnings and Precautions (5.1, 5.2)].*

Hypotension/Hypotension
Warn patients about the risk of hypotension and orthostatic hypotension and instruct patients to rise slowly from a supine or sitting position. Advise patients to notify their healthcare provider if they develop dizziness or lightheadedness *[see Warnings and Precautions (5.3)].*

Impulse Control Disorders and Compulsive Behaviors
Patients and their caregivers should be alerted to the possibility that patients may experience intense urges to spend money uncontrollably, intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking PARLODEL. Advise patients and their caregivers to inform their health care provider if they develop new or increased uncontrolled spending, gambling urges, sexual urges, or other urges while being treated with PARLODEL *[see Warnings and Precautions (5.5)].*

Falling Asleep During Activities of Daily Living
Advise patients of the risk of falling asleep while engaged in activities of daily living, including the operation of motor vehicles while taking PARLODEL. Ask patients about factors that may increase the risk for somnolence with dopaminergic therapy, such as concomitant sedating drugs or the presence of a sleep disorder.

If symptoms of somnolence or sudden sleep onset occur, advise patients not to drive or perform potentially dangerous activities while taking PARLODEL *[see Warnings and Precautions (5.6)].*

Visual Impairment in Patients with Prolactin-secreting Adenomas
Advise patients that PARLODEL treatment of a macroprolactinoma may lead to visual impairment.If patients experience visual impairment, they should seek immediate medical attention *[see Warnings and Precautions (5.7)]*.

Withdrawal Adverse Reactions After Rapid Dosage Reduction or Discontinuation in Patients with Patients with Idiopathic or Postencephalitic Parkinson's Disease or Acromegaly

Advise patients with with idiopathic or postencephalitic Parkinson's disease or acromegaly to contact their health care provider if they wish to discontinue PARLODEL or decrease the PARLODEL dosage because suddenly stopping PARLODEL can lead to withdrawal symptoms such as fever, muscular rigidity, altered consciousness, apathy, anxiety, depression, fatigue, insomnia, sweating, or pain *[see Warnings and Precautions (5.11)]*.

Pregnancy

Advise patients to notify their health care provider if they suspect they are pregnant, become pregnant, or intend to become pregnant during PARLODEL therapy. A pregnancy test should be done if there is any suspicion of pregnancy and continuation of PARLODEL treatment should be discussed with their health care provider *[see Use in Specific Populations (8.1)].*

Manufactured for:

**Esjay Pharma LLC**

East Windsor, NJ 08520, USA

Made in India

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