EMERGENCY OVERVIEW
Each Bromocriptine mesylate capsules USP 5 mg, intended for oral administration contains 5 mg of Bromocriptine mesylate and excipients generally considered to be non-toxic and non-hazardous in small quantities and under conditions of normal occupational exposure.

Section 1. IDENTIFICATION OF THE PRODUCT

Product Name: Bromocriptine mesylate capsules USP 5 mg
Active Pharmaceutical Ingredient: Bromocriptine mesylate
Formula: C_{32}H_{40}BrN_{5}O_{5}.CH_{4}SO_{3}
Chemical Name: Ergotaman-3´,6´,18-trione, 2-bromo-12´-hydroxy-2´-(1-methylethyl)-5´-(2-methylpropyl)-, (5´α)-mono-methanesulfonate (salt)

Mechanism of Action: Bromocriptine mesylate is a dopamine receptor agonist, which activates post-synaptic dopamine receptors. The dopaminergic neurons in the tuberoinfundibular process modulate the secretion of prolactin from the anterior pituitary by secreting a prolactin inhibitory factor (thought to be dopamine); in the corpus striatum the dopaminergic neurons are involved in the control of motor function. Clinically, bromocriptine significantly reduces plasma levels of prolactin in patients with physiologically elevated prolactin as well as 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. Experiments have demonstrated that
bromocriptine induces long lasting stereotyped behavior in rodents and turning behavior in rats having 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 mesylate is a nonhormonal, nonestrogenic agent that inhibits the secretion of prolactin in humans, with little or no effect on other pituitary hormones, except in patients with acromegaly, where it lowers elevated blood levels of growth hormone in the majority of patients.

**Manufacturer / supplier identification**

- **Company:** Cadila Healthcare Ltd. Ahmedabad, India
- **Address:** Sarkhej – Bavla. N.H. 8A, Moraiya. Tal. Sanand.
- **Dist. Ahmedabad – 382210. State: Gujarat. India**
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- **Emergency Telephone No.:** Tel.: +91 79 6868100

**Therapeutic Category:**

**Indications:**

**Hyperprolactinemia-Associated Dysfunctions:**

Bromocriptine mesylate tablets and capsules are indicated for the treatment of dysfunctions associated with hyperprolactinemia including amenorrhea with or without galactorrhea, infertility or hypogonadism. Bromocriptine treatment is indicated in patients with prolactin-secreting adenomas, which may be the basic underlying endocrinopathy contributing to the above clinical presentations. Reduction in tumor size has been demonstrated in both male and female patients with macroadenomas. In cases where adenectomy is elected, a course of bromocriptine mesylate tablets and/or capsules therapy may be used to reduce the tumor mass prior to surgery.

**Acromegaly:**

Bromocriptine mesylate tablets and capsules therapy is indicated in the treatment of acromegaly. Bromocriptine therapy, alone or as adjunctive therapy with pituitary irradiation or surgery, reduces serum growth hormone by 50% or more in approximately ½ of patients treated, although not usually to normal levels.

Since the effects of external pituitary radiation may not become maximal for several years, adjunctive therapy with bromocriptine offers potential benefit before the effects of irradiation are manifested.

**Parkinson’s Disease:**
Bromocriptine mesylate tablets or capsules are indicated in the treatment of the signs and symptoms of idiopathic or postencephalitic Parkinson’s disease. As adjunctive treatment to levodopa (alone or with a peripheral decarboxylase inhibitor), bromocriptine therapy may provide additional therapeutic benefits in those patients who are currently maintained on optimal dosages of levodopa, those who are beginning to deteriorate (develop tolerance) to levodopa therapy, and those who are experiencing “end of dose failure” on levodopa therapy. Bromocriptine therapy may permit a reduction of the maintenance dose of levodopa and, thus may ameliorate the occurrence and/or severity of adverse reactions associated with long-term levodopa therapy such as abnormal involuntary movements (e.g., dyskinesias) and the marked swings in motor function (“on-off” phenomenon). Continued efficacy of bromocriptine therapy during treatment of more than 2 years has not been established.

Data are insufficient to evaluate potential benefit from treating newly diagnosed Parkinson’s disease with bromocriptine. Studies have shown, however, significantly more adverse reactions (notably nausea, hallucinations, confusion and hypotension) in bromocriptine-treated patients than in levodopa/carbidopa treated patients. Patients unresponsive to levodopa are poor candidates for bromocriptine therapy.

**Recommended use:**

**Nursing Mothers:**
Bromocriptine should not be used during lactation in post-partum women.

**Pediatric Use:**
The safety and effectiveness of bromocriptine for the treatment of prolactin-secreting pituitary adenomas have been established in patients age 16 to adult. No data are available for bromocriptine use in pediatric patients under the age of 8 years. A single 8-year old patient treated with bromocriptine for a prolactin-secreting pituitary macroadenoma has been reported without therapeutic response.

The use of bromocriptine for the treatment of prolactin-secreting adenomas in pediatric patients in the age group 11 to under 16 years is supported by evidence from well-controlled trials in adults, with additional data in a limited number (n=14) of children and adolescents 11 to 15 years of age with prolactin-secreting pituitary macro- and microadenomas who have been treated with bromocriptine. Of the 14 reported patients, 9 had successful outcomes, 3 partial responses, and 2 failed to respond to
bromocriptine treatment. Chronic hypopituitarism complicated macroadenoma treatment in 5 of the responders, both in patients receiving bromocriptine alone and in those who received bromocriptine in combination with surgical treatment and/or pituitary irradiation.

**Geriatric Use:**
Clinical studies for bromocriptine did not include sufficient numbers of subjects aged 65 and over to determine whether the elderly respond differently from younger subjects. However, other reported clinical experiences, including post-marketing reporting of adverse events, have not identified differences in response or tolerability between elderly and younger patients. Even though no variation in efficacy or adverse reaction profile in geriatric patients taking bromocriptine has been observed, greater sensitivity of some elderly individuals cannot be categorically ruled out. In general, dose selection for an elderly patient should be cautious, starting at the lower end of the dose range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy in this population.

**Restriction on Use / Contraindications:**
Hypersensitivity to bromocriptine or to any of the excipients of bromocriptine mesylate capsules, uncontrolled hypertension and sensitivity to any ergot alkaloids. In patients being treated for hyperprolactinemia, bromocriptine mesylate tablets and capsules should be withdrawn when pregnancy is diagnosed (see PRECAUTIONS, Hyperprolactinemic States). In the event that bromocriptine is reinstituted to control a rapidly expanding macroadenoma (see PRECAUTIONS, Hyperprolactinemic States) and a patient experiences a hypertensive disorder of pregnancy, the benefit of continuing bromocriptine must be weighed against the possible risk of its use during a hypertensive disorder of pregnancy. When bromocriptine is being used to treat acromegaly, prolactinoma, or Parkinson’s disease in patients who subsequently become pregnant, a decision should be made as to whether the therapy continues to be medically necessary or can be withdrawn. If it is continued, the drug should be withdrawn in those who may experience hypertensive disorders of pregnancy (including eclampsia, preeclampsia, or pregnancy-induced hypertension) unless withdrawal of bromocriptine is considered to be medically contraindicated.
The drug should not be used during the post-partum period in women with a history of coronary artery disease and other severe cardiovascular conditions unless withdrawal is considered medically contraindicated. If the drug is used in the post-partum period the patient should be observed with caution.

SECTION 2. HAZARD(S) IDENTIFICATION

**Dosage and Administration**

**General:**

It is recommended that bromocriptine mesylate tablets and capsules be taken with food. Patients should be evaluated frequently during dose escalation to determine the lowest dosage that produces a therapeutic response.

**Hyperprolactinemic Indications:**

The initial dosage of bromocriptine mesylate tablets in adults is ½ to one 2½ mg scored tablet daily. An additional 2½ mg tablet may be added to the treatment regimen as tolerated every 2-7 days until an optimal therapeutic response is achieved. The therapeutic dosage ranged from 2.5-15 mg daily in adults studied clinically.

Based on limited data in children of age 11 to 15, the initial dose is ½ to one 2½ mg scored tablet daily. Dosing may need to be increased as tolerated until a therapeutic response is achieved. The therapeutic dosage ranged from 2.5-10 mg daily in children with prolactin-secreting pituitary adenomas.

In order to reduce the likelihood of prolonged exposure to bromocriptine mesylate tablets or capsules should an unsuspected pregnancy occur, a mechanical contraceptive should be used in conjunction with bromocriptine therapy until normal ovulatory menstrual cycles have been restored. Contraception may then be discontinued in patients desiring pregnancy.

Thereafter, if menstruation does not occur within 3 days of the expected date, bromocriptine therapy should be discontinued and a pregnancy test performed.

Virtually all acromegalic patients receiving therapeutic benefit from bromocriptine mesylate tablets and capsules also have reductions in circulating levels of growth hormone. Therefore, periodic assessment of circulating levels of growth hormone will, in most cases, serve as a guide in determining the therapeutic potential of bromocriptine. If, after a brief trial with bromocriptine therapy, no significant reduction in growth hormone levels has taken place, careful assessment of the clinical features of the
SAFETY DATA SHEET
BROMOCRIPTINE MESYLATE CAPSULES USP
Strength : 5 mg

Pack Style : NDC 68382-110-06 in bottle of 30 capsules
NDC 68382-110-01 in bottle of 100 capsules

Disease should be made, and if no change has occurred, dosage adjustment or discontinuation of therapy should be considered.
The initial recommended dosage is ½ to one 2½ mg bromocriptine mesylate tablet on retiring (with food) for 3 days. An additional ½ to 1 bromocriptine mesylate tablet should be added to the treatment regimen as tolerated every 3-7 days until the patient obtains optimal therapeutic benefit. Patients should be reevaluated monthly and the dosage adjusted based on reductions of growth hormone or clinical response. The usual optimal therapeutic dosage range of bromocriptine mesylate tablets and capsules varies from 20-30 mg/day in most patients. The maximal dosage should not exceed 100 mg/day.

Patients treated with pituitary irradiation should be withdrawn from bromocriptine therapy on a yearly basis to assess both the clinical effects of radiation on the disease process as well as the effects of bromocriptine therapy. Usually a 4-8 week withdrawal period is adequate for this purpose. Recurrence of the signs/symptoms or increases in growth hormone indicate the disease process is still active and further courses of bromocriptine should be considered.

**Parkinson’s Disease:**
The basic principle of bromocriptine mesylate therapy is to initiate treatment at a low dosage and, on an individual basis, increase the daily dosage slowly until a maximum therapeutic response is achieved. The dosage of levodopa during this introductory period should be maintained, if possible. The initial dose of bromocriptine is ½ of a 2½ mg tablet twice daily with meals. Assessments are advised at 2-week intervals during dosage titration to ensure that the lowest dosage producing an optimal therapeutic response is not exceeded. If necessary, the dosage may be increased every 14-28 days by 2½ mg/day with meals. Should it be advisable to reduce the dosage of levodopa because of adverse reactions, the daily dosage of bromocriptine, if increased, should be accomplished gradually in small (2½ mg) increments.
The safety of bromocriptine mesylate tablets and capsules has not been demonstrated in dosages exceeding 100 mg/day.

**Adverse Effects:**

**Clinical Trials Experience**

*Hyperprolactinemic Indications:*
The incidence of adverse effects is quite high (69%) but these are generally mild to moderate in degree. Therapy was discontinued in approximately 5% of patients because of adverse effects. These in decreasing order of frequency are: nausea (49%), headache (19%),
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Revision No.: 02

Dizziness (17%), fatigue (7%), lightheadedness (5%), vomiting (5%), abdominal cramps (4%), nasal congestion (3%), constipation (3%), diarrhea (3%) and drowsiness (3%).

A slight hypotensive effect may accompany bromocriptine mesylate treatment. The occurrence of adverse reactions may be lessened by temporarily reducing dosage to ½ a bromocriptine mesylate tablet 2 or 3 times daily. A few cases of cerebrospinal fluid rhinorrhea have been reported in patients receiving bromocriptine for treatment of large prolactinomas. This has occurred rarely, usually only in patients who have received previous transsphenoidal surgery, pituitary radiation, or both, and who were receiving bromocriptine for tumor recurrence. It may also occur in previously untreated patients whose tumor extends into the sphenoid sinus.

Acromegaly:
The most frequent adverse reactions encountered in acromegalic patients treated with bromocriptine 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%).

Less frequent adverse reactions (less than 2%) were: gastrointestinal bleeding, dizziness, exacerbation of Raynaud’s Syndrome, headache and syncope. Rarely (less than 1%) 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 have been reported.

Parkinson’s Disease:
In clinical trials in which bromocriptine was administered with concomitant reduction in the dose of levodopa/carbidopa, the most common newly appearing 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 which may be encountered include: 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 may include elevations in blood urea nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phosphatase and uric acid, which are usually transient and not of clinical significance.

**Adverse Reactions from Postmarketing Experience**

The following adverse reactions have been reported during postapproval use of bromocriptine mesylate (All Indications Combined). Because adverse reactions from spontaneous reports are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Psychiatric disorders**
Confusion, psychomotor agitation/excitation, hallucinations, psychotic disorders, insomnia, libido increase, hypersexuality.

**Nervous system disorders**
Headache, drowsiness, dizziness, dyskinesia, somnolence, paraesthesia, excess daytime somnolence, sudden onset of sleep.

**Eye disorders**
Visual disturbance, vision blurred.

**Ear and labyrinth disorders**
Tinnitus.

**Cardiac disorders**
Pericardial effusion, constrictive pericarditis, tachycardia, bradycardia, arrhythmia, cardiac valve fibrosis.

**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)

**Respiratory, thoracic and mediastinal disorders**
Nasal congestion, pleural effusion, pleural fibrosis, pleurisy, pulmonary fibrosis, dyspnoea.

**Gastrointestinal disorders**
Nausea, constipation, vomiting, dry mouth, diarrhoea, abdominal pain, retroperitoneal fibrosis, gastrointestinal ulcer, gastrointestinal haemorrhage.

**Skin and subcutaneous tissue disorders**
Allergic skin reactions, hair loss.

**Musculoskeletal and connective tissue disorders**
Leg cramps.

**General disorders and administration site conditions**
Fatigue, peripheral edema, a syndrome resembling Neuroleptic Malignant Syndrome on abrupt withdrawal of bromocriptine mesylate

### Over Dose Effect

The most commonly reported signs and symptoms associated with acute bromocriptine mesylate overdose are: nausea, vomiting, constipation, diaphoresis, dizziness, pallor, severe hypotension, malaise, confusion, lethargy, drowsiness, delusions, hallucinations, and repetitive yawning. The lethal dose has not been established and the drug has a very wide margin of safety. However, one death occurred in a patient who committed suicide with an unknown quantity of bromocriptine and chloroquine.

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 I.V. fluids. If satisfactory relief of hypotension cannot be achieved by using the above measures to their fullest extent, vasopressors should be considered.

There have been isolated reports of children who accidentally ingested bromocriptine mesylate. Vomiting, somnolence and fever were reported as adverse events. Patients recovered either spontaneously within a few hours or after appropriate management.

### Pregnancy Comments

**Teratogenic Effect:** Pregnancy Category B

Administration of 10-30 mg/kg of bromocriptine to 2 strains of rats on days 6-15 post coitum (p.c.) as well as a single dose of 10 mg/kg on day 5 p.c. interfered with nidation. Three mg/kg given on days 6-15 were without effect on nidation, and did not produce any anomalies. In animals treated from day 8-15 p.c., i.e., after implantation, 30 mg/kg produced increased prenatal mortality in the form of 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 treated with 30 mg/kg bromocriptine. No fetotoxic effects were found in offspring of dams treated during the peri- or post-natal period.

Two studies were conducted in rabbits (2 strains) to determine the potential to interfere with nidation. Dose levels of 100 or 300 mg/kg/day from day 1 to day 6 p.c. did not adversely affect nidation. The high dose was approximately 63 times the maximum human dose administered in controlled clinical trials (100 mg/day), based on body surface area. In New Zealand white rabbits some embryo mortality occurred at 300 mg/kg which was a reflection of overt maternal toxicity. Three studies were conducted in 2 strains of rabbits to determine the teratological potential of bromocriptine at dose levels of 3, 10, 30, 100, and 300 mg/kg given from day 6 to day 18 p.c. In 2 studies with the Yellow-silver strain, cleft palate was found in 3 and 2 fetuses at maternally toxic 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 produced. No teratological or embryo-toxic effects of bromocriptine were produced in any of 6 offspring from 6 monkeys at a dose level of 2 mg/kg.

Information concerning 1276 pregnancies in women taking bromocriptine has been collected. In the majority of cases, bromocriptine was discontinued within 8 weeks into pregnancy (mean 28.7 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 1276 pregnancies, there were 1088 full term deliveries (4 stillborn), 145 spontaneous abortions (11.4%), and 28 induced abortions (2.2%). Moreover, 12 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 15%.

The incidence of birth defects in the population at large ranges from 2%-4.5%. The incidence in 1109 live births from patients receiving bromocriptine is 3.3%.
There is no suggestion that bromocriptine contributed to the type or incidence of birth defects in this group of infants.

**Warnings & Precautions**

Since hyperprolactinemia with amenorrhea/galactorrhea and infertility has been found in patients with pituitary tumors, a complete evaluation of the pituitary is indicated before treatment with bromocriptine mesylate.

If pregnancy occurs during bromocriptine administration, careful observation of these patients is mandatory. 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 bromocriptine treatment has been reported to produce improvement in the visual fields of patients in whom nerve compression has occurred during pregnancy. The safety of bromocriptine treatment during pregnancy to the mother and fetus has not been established.

Bromocriptine mesylate has been associated with somnolence, and episodes of sudden sleep onset, particularly in patients with Parkinson’s disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported. Patients must be informed of this and advised not to drive or operate machines during treatment with bromocriptine. Patients who have experienced somnolence and/or an episode of sudden sleep onset must not drive or operate machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Symptomatic hypotension can occur in patients treated with bromocriptine for any indication. In post-partum studies with bromocriptine, decreases in supine systolic and diastolic pressures of greater than 20 mm and 10 mm Hg, respectively, have been observed in almost 30% of patients receiving bromocriptine. On occasion, the drop in supine systolic pressure was as much as 50-59 mm of Hg.

Since, especially during the first days of treatment, hypotensive reactions may occasionally occur and result in reduced alertness, particular care should be exercised when driving a vehicle or operating machinery.

While hypotension during the start of therapy with bromocriptine occurs in some patients, in rare cases serious adverse events, including hypertension, myocardial infarction, seizures, stroke, have been reported in postpartum women treated with bromocriptine mesylate. Hypertension have been reported.
sometimes at the initiation of therapy, but often developing in the second week of therapy; seizures have also been reported both with and without the prior development of hypertension; stroke have been reported mostly in post-partum patients whose prenatal and obstetric courses had been uncomplicated. Many of these patients experiencing seizures (including cases of status epilepticus) and/or strokes reported developing a constant and often progressively severe headache 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). Cases of acute myocardial infarction have also been reported.

Although a causal relationship between bromocriptine administration and hypertension, seizures, strokes, and myocardial infarction in post-partum women has not been established, use of the drug in patients with uncontrolled hypertension is not recommended. In patients being treated for hyperprolactinemia bromocriptine should be withdrawn when pregnancy is diagnosed. In the event that bromocriptine is re instituted to control a rapidly expanding macroadenoma and a patient experiences a hypertensive disorder of pregnancy, the benefit of continuing bromocriptine must be weighed against the possible risk of its use during a hypertensive disorder of pregnancy. When bromocriptine is being used to treat acromegaly or Parkinson’s disease in patients who subsequently become pregnant, a decision should be made as to whether the therapy continues to be medically necessary or can be withdrawn. If it is continued, the drug should be withdrawn in those who may experience hypertensive disorders of pregnancy (including eclampsia, preeclampsia, or pregnancy-induced hypertension) unless withdrawal of bromocriptine is considered to be medically contraindicated. Because of the possibility of an interaction between bromocriptine and other ergot alkaloids, the concomitant use of these medications is not recommended. Periodic monitoring of the blood pressure, particularly during the first weeks of therapy is prudent. If hypertension, severe, progressive, or unremitting headache (with or without visual disturbance), or evidence of CNS toxicity develops, drug therapy should be discontinued and the patient should be evaluated promptly. Particular attention should be paid to patients who have recently been treated or are on concomitant therapy with drugs that can alter blood pressure. Their concomitant use in the puerperium is not recommended.

Among patients on bromocriptine mesylate, particularly on long-term and high-dose treatment, pleural and pericardial effusions, as
well as pleural and pulmonary fibrosis and constrictive pericarditis, have been reported. Patients with unexplained pleuropulmonary disorders should be examined thoroughly and discontinuation of bromocriptine mesylate therapy should be considered. In those instances in which bromocriptine treatment was terminated, the changes slowly reverted towards normal.

In a few patients on bromocriptine mesylate, particularly on long-term and high-dose treatment, retroperitoneal fibrosis has been reported. To ensure recognition of retroperitoneal fibrosis at an early reversible stage it is recommended that its manifestations (e.g., back pain, edema of the lower limbs, impaired kidney function) should be watched in this category of patients. Bromocriptine mesylate medication should be withdrawn if fibrotic changes in the retroperitoneum are diagnosed or suspected.

**Precautions**

Safety and efficacy of bromocriptine have not been established in patients with renal or hepatic disease. Care should be exercised when administering bromocriptine mesylate therapy concomitantly with other medications known to lower blood pressure.

The drug should be used with caution in patients with a history of psychosis or cardiovascular disease. If acromegalic patients or patients with prolactinoma or Parkinson’s disease are being treated with bromocriptine during pregnancy, they should be cautiously observed, particularly during the post-partum period if they have a history of cardiovascular disease.

Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Hyperprolactinemic States:**

Visual field impairment is a known complication of macroprolactinoma. Effective treatment with bromocriptine leads to a reduction in hyperprolactinemia and often to a resolution of the visual impairment. In some patients, however, a secondary deterioration of visual fields may subsequently 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. In these cases the visual field defect may improve on reduction of bromocriptine dosage while there is some elevation of prolactin and some tumor re-expansion. Monitoring of visual fields in patients with macroprolactinoma is therefore recommended for an early recognition of secondary field loss due to chiasmal herniation and adaptation of drug dosage.
The relative efficacy of bromocriptine versus surgery in preserving visual fields is not known. Patients with rapidly progressive visual field loss should be evaluated by a neurosurgeon to help decide on the most appropriate therapy.

Since pregnancy is often the therapeutic objective in many hyperprolactinemic patients presenting with amenorrhea/galactorrhea and hypogonadism (infertility), a careful assessment of the pituitary is essential to detect the presence of a prolactin-secreting adenoma. Patients not seeking pregnancy, or those harboring large adenomas, should be advised to use contraceptive measures, other than oral contraceptives, during treatment with bromocriptine. Since pregnancy may occur prior to reinitiation of menses, a pregnancy test is recommended at least every 4 weeks during the amenorrheic period, and, once menses are reinitiated, every time a patient misses a menstrual period. Treatment with bromocriptine mesylate tablets or capsules should be discontinued as soon as pregnancy has been established. Patients must 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 bromocriptine treatment in patients with known macroadenomas has been associated with rapid regrowth of tumor and increase in serum prolactin in most cases.

Cerebrospinal fluid rhinorrhea has been observed in some patients with prolactin-secreting adenomas treated with bromocriptine mesylate.

Cold sensitive digital vasospasm has been observed in some acromegalic patients treated with bromocriptine. The response, should it occur, can be reversed by reducing the dose of bromocriptine and may be prevented by keeping the fingers warm. Cases of severe gastrointestinal bleeding from peptic ulcers have been reported, some fatal. Although there is no evidence that bromocriptine increases the incidence of peptic ulcers in acromegalic patients, symptoms suggestive of peptic ulcer should be investigated thoroughly and treated appropriately. Patients with a history of peptic ulcer or gastrointestinal bleeding should be observed carefully during treatment with bromocriptine.

Possible tumor expansion while receiving bromocriptine therapy has been reported in a few patients. Since the natural history of growth hormone secreting tumors is unknown, all patients should be carefully monitored and, if evidence of tumor expansion...
develops, discontinuation of treatment and alternative procedures considered.

**Parkinson’s Disease:**
Safety during long-term use for more than 2 years at the doses required for parkinsonism has not been established.
As with any chronic therapy, periodic evaluation of hepatic, hematopoietic, cardiovascular, and renal function is recommended. Symptomatic hypotension can occur and, therefore, caution should be exercised when treating patients receiving antihypertensive drugs.
High doses of bromocriptine may be associated with confusion and mental disturbances. Since parkinsonian patients may manifest mild degrees of dementia, caution should be used when treating such patients.
Bromocriptine administered alone or concomitantly with levodopa may cause hallucinations (visual or auditory). Hallucinations usually resolve with dosage reduction; occasionally, discontinuation of bromocriptine is required. Rarely, after high doses, hallucinations have persisted for several weeks following discontinuation of bromocriptine.
Postmarketing reports suggest that patients treated with anti-Parkinson medications can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges. Patients may be unable to control these urges while taking one or more of the medications that are generally used for the treatment of Parkinson’s disease and that increase central dopaminergic tone, including bromocriptine mesylate. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with bromocriptine mesylate. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking bromocriptine mesylate.
As with levodopa, caution should be exercised when administering bromocriptine to patients with a history of myocardial infarction who have a residual atrial, nodal, or ventricular arrhythmia.
Retroperitoneal fibrosis has been reported in a few patients receiving long-term therapy (2-10 years) with bromocriptine mesylate in doses ranging from 30-140 mg daily. Epidemiological studies have shown that patients with Parkinson’s disease have a higher risk (2-approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson’s disease or other factors, such as drugs used to treat Parkinson’s disease, is unclear. For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using bromocriptine mesylate for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g. dermatologists).

Discontinuation of bromocriptine mesylate should be undertaken gradually whenever possible, even if the patient is to remain on L-dopa. 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 dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

**Drug Interactions:**

The risk of using bromocriptine in combination with other drugs has not been systematically evaluated, but alcohol may potentiate the side effects of bromocriptine. Bromocriptine may interact with dopamine antagonists, butyrophenones, and certain other agents. Compounds in these categories result in a decreased efficacy of bromocriptine: phenothiazines, haloperidol, metoclopramide, pimozide. Bromocriptine is a substrate of CYP3A4. Caution should therefore be used when coadministering drugs which are strong inhibitors of this enzyme (such as azole antifungal agents, HIV protease inhibitors). The concomitant use of macrolide antibiotics such as erythromycin was shown to increase the plasma levels of bromocriptine (mean AUC and Cmax values increased 3.7-fold and 4.6-fold, respectively). 1 The concomitant treatment of acromegalic patients with bromocriptine and octreotide led to increased plasma levels of bromocriptine (bromocriptine AUC increased about 38%). 4 Concomitant use of bromocriptine mesylate with other ergot alkaloids is not recommended. Dose adjustment may be necessary in those cases where high doses of bromocriptine are being used (such as Parkinson’s disease indication).
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Section 3. COMPOSITION / INFORMATION ON INGREDIENTS

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<th>Component</th>
<th>Exposure limit</th>
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<td>Lactose monohydrate</td>
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<tr>
<td>Magnesium stearate</td>
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<td>Maleic Acid</td>
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<td>hypromellose</td>
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<td>1310-58-3</td>
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<td>Titanium dioxide</td>
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<td><strong>Capsule Shell</strong></td>
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<td>Shellac</td>
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<td>Strong ammonia solution</td>
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</table>

Section 4. FIRST-AID MEASURES

General
Remove from exposure. Remove contaminated Clothing. Person developing serious hypersensitivity reaction must receive medical attention

Inhalation
remove to fresh air. If not breathing give artificial respiration or give oxygen by trained personnel

Skin contact
immediately wash skin with plain water and plenty of soap for at least 15 minutes. Remove contaminated clothing. Get medical attention if symptoms occur. Wash clothing before reuse.

Eye contact
hold eyelids apart and flush eyes with plenty of water for at least 15 minutes. Have eyes examined and tested by medical professional. Wash out mouth with water provided the person is conscious. Never give anything by mouth to an unconscious person. Get medical attention. Do not induce vomiting unless directed to do so by medical professional.
Section 5. FIRE FIGHTING MEASURES

Flash point: Not Found
Upper Flammable limit: Not Found
Lower flammable limit: Not Found
Auto ignition temperature: not found
Extinguishing media: Water Spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and material
Fire & Explosion hazard: This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with the dry material to dissipate the potential build up of static electricity.
Fire fighting procedure: As with all fires, evacuate personnel to a safe area. Fire fighter should use self-contained breathing equipment and protective clothing.

Section 6. ACCIDENTAL RELEASE MEASURES

Small Spill: Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.
Large Spill: Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.
Spill Clean Up Procedures Use proper personal protective equipment and clothing. Shut off the source of the spill or leak if it is safe to do so. Scoop or shovel spilled material into a suitable labeled open head drum. Secure the drum cover and move the container to a safe holding area. Wash spill area thoroughly with soapy water.
Treatment and Disposal Decontaminate equipment. Dispose of protective clothing with spilled material.
Environmental precautions Avoid release to the environment. Prevent further leakage or spillage if safe to do so. Avoid discharge into drains, water courses or onto the ground. Inform appropriate managerial or supervisory personnel of all environmental releases.

Section 7. HANDLING AND STORAGE

Storage Store at 20° to 25°C (68° to 77° F); in tight, light-resistant container.
Precautions for safe handling
Dispense in a tight, light-resistant container. Keep locked up. Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk; evaporate the residue under a fume hood. Ground all equipment containing material. Do not ingest. Do not breathe dust. Wear suitable protective clothing. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes.

Section 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Engineering controls
Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection
Safety glasses. Labcoat.

Eye/face protection
If contact is likely, safety glasses with side shields are recommended.

Protective Clothing
Protective clothing is not normally necessary, however it is good practice to use apron.

Personal Protection in Case of a Large Spill
Splash goggles. Full suit. Boots. Gloves. Suggested protective clothing might not be sufficient; consult a specialist before handling this product.

Exposure Limit
Data not available

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance

Physical state
Capsules

Description
Bromocriptine Mesylate Capsules USP, 5 mg are white to off-white powder filled in size “3” empty Cellulose capsules with tan colored cap printed with “ZA 17” in black ink and white colored body printed with “5 mg” in black ink

Pure/Mixture
Mixture

Bromocriptine mesylate, USP is white or slightly colored, fine crystalline powder and odorless or having a weak, characteristic odor.
Section 10. STABILITY AND REACTIVITY

Stability: The product is stable.

Section 11. TOXICOLOGICAL INFORMATION

Carcinogenesis, Mutagenesis, Impairment of Fertility
50 mg/kg/day. A 100-week study in rats was conducted using dietary levels equivalent to oral doses of 1.7, 9.8, and 44 mg/kg/day. The highest doses tested in mice and rats were approximately 2.5 and 4.4 times, respectively, the maximum human dose administered in controlled clinical trials (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 occurring 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.

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 obtained in any of these tests.

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

Section 12. ECOLOGICAL INFORMATION

Avoid release into the environment.
Runoff from fire control or dilution water may cause pollution.

Section 13. DISPOSAL CONSIDERATION

All waste must be handled in accordance with local, state and federal regulations.
Legislation addressing waste disposal requirements may differ by country, state and/or territory. Each user must refer to laws operating in their area.
Section 14. TRANSPORT INFORMATION

The product is not hazardous when shipping via air (IATA), ground (DOT), or sea (IMDG).

Section 15. REGULATORY INFORMATION

Generic Medicine, ANDA Number – 78-899

Section 16. OTHER INFORMATION

NFPA (National Fire Protection Association (U.S.A.) Rating: These ratings are based on NFPA code 704 and are intended for use by emergency personnel to determine the immediate hazards of a material

<table>
<thead>
<tr>
<th>NFPA (USA)</th>
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<tbody>
<tr>
<td>health</td>
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<tr>
<td>Flammability</td>
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<tr>
<td>Instability</td>
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Date of issue: November 30, 2017. Supersedes edition: 01

The information presented in the safety data sheet is, to the best our knowledge, accurate and reliable. It characterizes the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product,