PRODUCT MONOGRAPH

MYLAN-BROMAZEPAM

(Bromazepam Tablets)

1.5 mg

Anxiolytic - Sedative

Mylan Pharmaceuticals ULC
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1.5 mg

THERAPEUTIC CLASSIFICATION
Anxiolytic - Sedative

ACTION AND CLINICAL PHARMACOLOGY
Bromazepam is a benzodiazepine with anxiolytic and sedative properties which are of value in the symptomatic relief of pathological anxiety in psychoneurotic patients.

Orally administered bromazepam is completely absorbed and peak blood levels are achieved 1 to 4 hours after administration. Bromazepam has a mean serum half-life of 12 hours (8 to 19 hours). Over a 72 hour interval, 69% of a 12 mg oral dose was recovered in the urine, in the form of conjugated 3-hydroxybromazepam and conjugated 2-(2-amino-5-bromo-3-hydroxybenzoyl)-pyridine.

A comparative two-way bioavailability study was conducted to compare MYLAN-BROMAZEPAM (bromazepam) 6 mg tablets against a Canadian Reference Brand Product of bromazepam 6 mg tablets. The pharmacokinetic data calculated for the MYLAN-BROMAZEPAM and Reference product tablet formulations is tabulated below:

Parameter	**Test Product**	**Reference Product**	**Ratio of Geometric Means (%)**
AUC_t (ng.h/mL)	3714.50* 3904.77 (1136.48)**	3640.95* 3798.62 (1145.35)**	102.48
AUC_i (ng.h/mL)	4023.87* 4213.14 (1275.81)**	3944.19* 4186.73 (1430.72)**	101.12
C_{max} (ng/mL)	183.09* 190.24 (52.82)**	175.92* 179.01 (37.26)**	104.17
T_{max} (h)	1.43 (0.98)**	1.43 (1.18)**	---
$T_{1/2}$ (h)	20.27 (6.74)**	23.01 (10.29)**	---

* Geometric Mean
** Arithmetic Mean (CV)

INDICATIONS AND CLINICAL USE

MYLAN-BROMAZEPAM (bromazepam) is useful for the short-term, symptomatic relief of manifestations of excessive anxiety in patients with anxiety neurosis.

CONTRAINDICATIONS

MYLAN-BROMAZEPAM (bromazepam) is contraindicated in patients with known hypersensitivity to benzodiazepines and in patients with myasthenia gravis.

WARNINGS

MYLAN-BROMAZEPAM (bromazepam) is not recommended for use in patients with depressive disorders or psychosis. Patients should be advised against the concurrent use of alcohol and other CNS depressant drugs.

Pediatric use: Because of the lack of sufficient clinical experience, bromazepam is not recommended for use in patients less than 18 years of age.

Driving and Hazardous Activities: Since bromazepam has a central nervous system depressant effect, patients should be warned against driving, operating dangerous machinery, or engaging in other hazardous activities requiring mental alertness and physical coordination and should be cautioned that the effects of alcohol on such activities may be increased.

Use in Pregnancy: The safety of use of bromazepam in pregnancy has not been established. Therefore, bromazepam should not be used during pregnancy. Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines chlordiazepoxide and diazepam, and meprobamate, during the first trimester of pregnancies. Since bromazepam is also a benzodiazepine derivative, its administration is rarely justified in women of child-bearing potential. If the drug is prescribed to a woman of child-bearing potential, she should be warned to consult her physician regarding discontinuation of the drug if she plans to become or suspects that she is pregnant.

Use by Nursing Mothers: Bromazepam and its metabolites are probably excreted in human milk. Therefore, this drug should not be given to nursing mothers.

PRECAUTIONS

Use in the Elderly: Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to CNS depression after even low doses of benzodiazepines. Therefore, medication should be initiated in these patients with very low initial doses, and increments should be made gradually, depending on the response of the patient, in order to avoid over

sedation or neurological impairment. The initial dose for the elderly or debilitated patients should not exceed 3 mg.

Dependence Liability: MYLAN-BROMAZEPAM (bromazepam) should not be administered to individuals prone to drug abuse.

Caution should be observed in all patients who are considered to have potential for psychological dependence.

Withdrawal symptoms similar to those occurring with other drugs of this class including alcohol, have been observed after abrupt discontinuation of the drug. These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and memory impairment. Since these symptoms are similar to those for which the patient is being treated, it may appear that he has suffered a relapse upon discontinuation of the drug. It is suggested that the drug should be withdrawn gradually, if the individual is suspected of being dependent, or the drug perhaps has been used in prolonged high doses.

Mental and Emotional Disorders: It should be recognized that suicidal tendencies may be present in patients with emotional disorders and that protective measures and appropriate treatment may be necessary and should be instituted without delay.

Since excitement and other paradoxical reactions can result from the use of anxiolytic-sedatives in psychotic patients, bromazepam should not be used in ambulatory patients suspected of having psychotic tendencies.

As with other benzodiazepines, bromazepam should not be used in individuals with physiological anxiety or normal stresses of daily living, but only in the presence of disabling manifestations of an appropriate pathological anxiety disorder. These drugs are not effective in patients with characterological and personality disorders or those with obsessive-compulsive disorders. Bromazepam is also not recommended for management of depressive or psychotic disorders.

Impaired Hepatic or Renal Function: In patients with impaired hepatic or renal function, it is recommended to initiate therapy, if necessary, at a very low dose and to increase the dosage only to the extent that such an increase is compatible with the degree of residual function of these organs. Such patients should be followed closely and have periodic laboratory assessments.

Laboratory Tests: If bromazepam should be administered for repeated cycles of therapy, periodic blood counts and liver function tests are advisable.

Drug Interactions: Bromazepam may potentiate or interact with the effects of other CNS-acting drugs such as alcohol, narcotics, barbiturates, non-barbiturate hypnotics, antihistamines, phenothiazines, thioxanthenes, butyrophenones, monoamine oxidase inhibitors, tricyclic antidepressants and anticonvulsants. Therefore, if bromazepam is to be combined with other drugs acting on the CNS, careful consideration should be given to the pharmacology of the agent

involved because of the possible additive or potentiation of drug effects. Patients should also be advised against the simultaneous use of other CNS depressant drugs and should be cautioned not to take alcohol during the administration of bromazepam because of the potentiation of effects that might occur.

ADVERSE REACTIONS

The most frequently reported adverse reactions with bromazepam have been drowsiness, ataxia, and dizziness. Release of hostility and other paradoxical effects such as irritability and excitability are known to occur with the use of benzodiazepines.

Other side effects less frequently reported, listed by body systems, include the following:

Neurologic: blurred vision, headache, seizures, slurred speech, difficulty in depth perception.

Psychiatric: agitation, mental confusion, depression, irritability, nervousness, sleep disorders, euphoria, lethargy, stupor.

Gastrointestinal: dry mouth, nausea, non-specific gastrointestinal disturbances, vomiting.

Musculoskeletal: muscle spasm, muscle weakness.

Cardiovascular: hypotension, palpitations, tachycardia.

Dermatologic: pruritus, rash.

Genitourinary: incontinence, change in libido.

Hematologic: decreased hemoglobin and hematocrit, increased and decreased WBC.

Hepatic: elevations of alkaline phosphatase, bilirubin, AST (SGOT), ALT (SGPT).

Miscellaneous Blood chemistry: increased and decreased blood sugar levels.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Overdosage manifestations include drowsiness, somnolence, ataxia, impaired vision, depressed reflexes and finally coma. Hypotension and respiratory depression may occur with large overdoses.

Treatment: Vital signs should be monitored and general supportive measures should be employed as indicated. Gastric lavage should be instituted as soon as possible. Vomiting may be induced if the patient is fully awake. The value of dialysis has not been determined.

As is frequently the case in intentional overdose, the probability of multiple agents having been ingested should be considered.

DOSAGE AND ADMINISTRATION

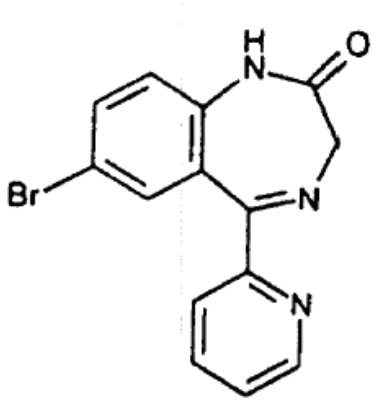
The dosage of MYLAN-BROMAZEPAM (bromazepam) must be individualised and carefully titrated in order to avoid excessive sedation or mental and motor impairment. Short course of treatment should usually be the rule for the symptomatic relief of excessive anxiety and the initial course of treatment should not last longer than one week without reassessment of the need for a limited extension. If necessary, drug dosage can be adjusted after one week of treatment. Initially, not more than one week's supply of the drug should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to a short course of therapy.

Usual Adult Dosage: The recommended initial adult daily dosage is 6 to 18 mg in equally divided doses, depending on the severity of symptoms and response of the patient. Treatment should be initiated by lower doses and adjusted as necessary. The optimal dosage may range from 6 to 30 mg daily in individual patients, in divided doses. Doses up to 60 mg daily may be used in exceptional cases.

Elderly and Debilitated Patients: The initial daily dose in these patients should not exceed 3 mg in divided doses. This dosage can be carefully adjusted, depending on tolerance and response of the patient.

PHARMACEUTICAL INFORMATION

Drug Substance:
Proper Name: Bromazepam
Chemical Name: 7-Bromo-1,3-dihydro-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one
Structural Formula:



Molecular Formula: $C_{14}H_{10}BrN_3O$
Molecular Weight: 316.16
Description: Bromazepam is an off white/pale yellow, crystalline, odorless powder, free of visible particulate matter with a melting point between 237 and 238.5ºC. It is practically insoluble in water; sparingly soluble in dichloromethane and in ethanol (96%); soluble in alcohol and in methylene chloride.

Composition: MYLAN-BROMAZEPAM tablets contain 1.5 of Bromazepam. The non-medicinal ingredients are lactose, magnesium stearate, microcrystalline cellulose, starch and talc

Stability and Storage Recommendations: Store between 15ºC to 30ºC.

AVAILABILITY OF DOSAGE FORMS

MYLAN-BROMAZEPAM (bromazepam) is available as follows:

- MYLAN-BROMAZEPAM 1.5 mg Tablets are white, round, flat bevelled edged with "B" bisect "1.5" on one side and "G" on the other.

The 1.5 mg strength is available in bottles of 100's.

PHARMACOLOGY

Bromazepam is a benzodiazepine with CNS depressant properties. In laboratory animals, it has shown anti-anxiety, sedative, muscle relaxant and anticonvulsant properties. In a "conflict" test, bromazepam was active in restoring suppressed lever-pressing behaviour (punishment induced suppression) at a minimum effective dose (MED) of 0.16 mg/kg orally in rats. This activity was demonstrated over a dose range which did not involve either depression or stimulation of unpunished control patterns of lever-pressing behaviour. At 2.5 mg/kg, a dose 16 times greater than the MED, bromazepam produced the first decrease in unpunished lever-pressing. In rats, utilizing the Sidman continuous avoidance test, an MED of 1.7 mg/kg i.p. decreased the rate of avoidance of shock, and 5.6 mg/kg i.p. prevented the rat from turning off the shock. A marked reduction in aggressive behaviour was observed in vicious cynomolgus monkeys after an oral dose of 1 mg/kg and a taming effect at a dose of 2.5 mg/kg p.o. In the inclined screen test in mice the ED_{50} for bromazepam was 30 mg/kg p.o. In cats, the minimal effective taming dose of bromazepam was 0.2 mg/kg p.o.
Doses of 0.72 to 0.94 mg/kg p.o. of bromazepam protected mice against metrazol (125 mg/kg) induced convulsions. Bromazepam administered at doses of 3.90 to 34.2 mg/kg and 65 to 133 mg/kg p.o. protected mice against maximal and minimal electroshock-induced convulsions, respectively. A single dose of bromazepam (0.25 to 0.50 mg/kg p.o.) produced sedation or ataxia and modified the sleep cycle in cats. An increase in the amplitude of the electrical patterns of the caudate nucleus was observed.

A decrease in blood pressure was observed after the intravenous administration of bromazepam to anesthetized cats (1 mg/kg) and dogs (5 mg/kg). However, in hypertensive rats little or no antihypertensive effect was detected. Bromazepam inhibited no diuretic, anti-obesity, anti-diabetic or anti-emetic activity.

Metabolism:
The metabolism of bromazepam was studied in the mouse, rat and dog using ^{14}C labelled drug. The quantitative determination of the metabolites indicates that marked differences in the excretion patterns exist in these species. In the mouse and dog the major metabolite is 3-hydroxybromazepam, although it is only present as a minor metabolite in the rat. Both 2-(2-amino-5-bromobenzoyl) pyridine and its 3-hydroxy derivative are found as metabolites of bromazepam in all 3 species. In the dog, a separate biotransformation occurs such that the nitrogen atom, at the 4-position of the diazepam ring, is oxidized to bromazepam 4-oxide. In rats, over 80% of an administered oral dose of bromazepam is excreted in 4 days, whereas in the dog, excretion is much slower. In rats, biliary excretion and in dogs, urinary excretion is the predominant route of elimination.

TOXICOLOGY

Acute Toxicity:	LD_{50} (mg/kg)			
	p.o.	i.p.	s.c.	i.v.
mice (CF1)	2350	550	7400	13.7
rats-mature (Wistar)	3050	2300	--	--
rats-neonatal (Wistar)	110	--	--	--

rabbits (Wistar)	1690	--	--	--
dogs	≥1280	--	--	--

Signs of toxicity included decreased motor activity, ataxia, loss of righting reflex and lacrimation.

Chronic Toxicity: Bromazepam was administered in the diet to rats for a period of 18 months at doses of 0, 5, 20 and 80 mg/kg/day. No deviations from normal were observed except for an increase in the liver weight at necropsy at the time of the interim kill (18 months). Differences were not found in animals killed at the end of the study (24 months, after 6 months recovery) except for an increase in the ratio of liver to body weight. Histopathological examination revealed centrolobular hepatocellular hypertrophy in the treated groups.

Daily doses of 0, 5, 20 and 80 mg/kg were administered in the diet to dogs for a period of one year. In the high dose group, untoward effects were slight-to-moderate sedation and ataxia, which decreased as the study progressed. Isolated brief convulsive seizures were observed and an occasional elevation in serum alkaline phosphatase, a borderline increase in SGPT and a slight increase in liver weights occurred in a few dogs in the 80 mg/kg dosage group.

Reproductive Studies: Reproductive, teratological, perinatal and postnatal studies in rats receiving bromazepam at levels of 5 and 50 mg/kg/day p.o. revealed an increase in fetal mortality in the 50 mg/kg group. However, a second reproductive study, in which rats were administered either 10 or 25 mg/kg/day, revealed an increase in the stillbirth rate and a reduction in pup survival at both doses during the first 4 days following delivery. In another rat study, the daily oral administration of 1 mg/kg through two successive matings did not affect the reproductive processes. Bromazepam at doses of 10 mg/kg/day produced a slight decrease in the number of pregnancies and in the post-partum survival of the offsprings following the second matings. When 100 mg/kg/day was given through 3 successive matings, a decrease in the number of pregnancies in the parent generation and in the post-partum survivability of the offsprings was observed in all instances. Bromazepam was given to pregnant rabbits at doses of 5 and 50 mg/kg/day p.o. The following effects were noted: a reduction in maternal weight gain, a reduction in fetal weight, and an increase in the incidence of resorptions in both treated groups. In a second study in rabbits, at dose levels of 5 and 80 mg/kg/day p.o., no teratogenic effects were observed. Pregnant mice were administered bromazepam orally by stomach tube from day 7 through 13 or 16 of pregnancy at dose levels of 5, 10, 50 and 125 mg/kg/day. No teratogenic effects were detected.

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