CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

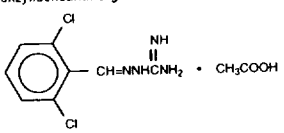
74517

DRAFT FINAL PRINTED LABELING

FINAL PRINTED INSERT

GUANABENZ ACETATE TABLETS, USP

DESCRIPTION:
Guanabenz acetate, an antihypertensive agent for oral administration, is an aminoguanidine derivative, 2,6-dichlorobenzylideneamino-guanidine acetate, and its structural formula is:



$C_8H_8Cl_2N_4 \cdot C_2H_4O_2$ M.W. 291.14

It is white to almost white powder having not more than a slight odor. Sparingly soluble in water and in 0.1 N hydrochloric acid; soluble in alcohol and in propylene glycol. Each tablet of guanabenz acetate is equivalent to 4 mg or 8 mg of free guanabenz base. The inactive ingredients present are anhydrous lactose, brown iron oxide, colloidal silicon dioxide, FD&C Blue No.1 Aluminum Lake, magnesium stearate, microcrystalline cellulose, pregelatinized starch and sodium starch glycolate.

Guanabenz acetate tablets, for oral administration, contain 4 mg or 8 mg guanabenz (base).

CLINICAL PHARMACOLOGY:
Guanabenz acetate is an orally active central alpha-2 adrenergic agonist. Its antihypertensive action appears to be mediated via stimulation of central alpha adrenergic receptors, resulting in a decrease of sympathetic outflow from the brain at the bulbar level to the peripheral circulatory system.

PHARMACOKINETICS
In human studies, about 75% of an orally administered dose of guanabenz acetate is absorbed and metabolized with less than 1% of unchanged drug recovered from the urine. Peak plasma concentrations of unchanged drug occur between two and five hours after a single oral dose. The average half-life for guanabenz is about 6 hours. The site or sites of metabolism of guanabenz have not been determined. The effect of meals on the absorption of guanabenz acetate tablets has not been studied.

PHARMACODYNAMICS
The onset of the antihypertensive action of guanabenz begins within 60 minutes after a single oral dose and reaches a peak effect within two to four hours. The effect of an acute single dose is reduced appreciably six to eight hours after administration, and blood pressure approaches baseline values within 12 hours of administration.

The acute antihypertensive effect of guanabenz occurs without major changes in peripheral resistance, but its chronic effect appears to be a decrease in peripheral resistance. A decrease in blood pressure is seen in both the supine and standing positions without alterations of normal postural mechanisms, so that postural hypotension has not been observed. Guanabenz decreases pulse rate by about 5 beats per minute. Cardiac output and left ventricular ejection fraction are unchanged during long-term therapy.

In clinical trials, guanabenz acetate, given orally to hypertensive patients, effectively controlled blood pressure without any significant effect on glomerular filtration rate, renal blood flow, body fluid volume or body weight. Guanabenz given parenterally to dogs has produced a natriuresis. Similarly, hypertensive subjects, 24 hours after salt loading, have shown a decrease in blood pressure and a natriuresis (5% to 240% increase in sodium excretion) following a single oral dose of guanabenz acetate. After seven consecutive days of administration and effective blood-pressure control, no significant change on glomerular filtration rate, renal blood flow, or body weight was observed. However, in clinical trials of six to thirty months duration, hypertensive patients with effective blood-pressure control by guanabenz lost one to four pounds of body weight. The mechanism of this weight loss has not been established. Tolerance to the antihypertensive effect of guanabenz has not been observed.

During long-term administration of guanabenz, there is a small decrease in serum cholesterol and total triglycerides without any change in the high-density lipoprotein fraction. Plasma norepinephrine, serum dopamine beta-hydroxylase, and plasma renin activity are decreased during chronic administration of guanabenz. No changes in serum-electrolytes, uric acid, blood-urea nitrogen, calcium, or glucose have been observed.

Guanabenz and hydrochlorothiazide have been shown to have at least partially additive effects in patients not responding adequately to either drug alone.

INDICATIONS AND USAGE:
Guanabenz acetate tablets are indicated in the treatment of hypertension. It may be employed alone or in combination with a thiazide diuretic.

CONTRAINDICATIONS:
Guanabenz acetate is contraindicated in patients with a known sensitivity to the drug or any of the tablet ingredients.

PRECAUTIONS:
General:
1. Sedation: Guanabenz causes sedation or drowsiness in a large fraction of patients. When guanabenz is used with centrally active depressants, such as phenothiazines, barbiturates, and benzodiazepines, the potential for additive sedative effects should be considered.

2. Patients with vascular insufficiency: Guanabenz, like other antihypertensive agents, should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or severe hepatic or renal failure.

3. Rebound: Sudden cessation of therapy with central alpha agonists like guanabenz may rarely result in "overshoot" hypertension and more commonly produces an increase in serum catecholamines and subjective symptomatology.

4. Patients with hepatic impairment: The disposition of orally administered guanabenz acetate is altered in patients with alcohol- induced liver disease. Mean plasma concentrations of guanabenz acetate were higher in these patients than in healthy subjects. The clinical significance of this finding is unknown. However, careful monitoring of blood pressure is suggested when guanabenz is administered to patients with hypertension and coexisting chronic hepatic dysfunction.

5. Patients with renal impairment: The disposition of orally administered guanabenz acetate is altered modestly in patients with renal impairment. Guanabenz's half-life is prolonged and clearance decreased, more so in patients on hemodialysis. The clinical significance of these findings is unknown. Careful monitoring of blood pressure during guanabenz dose titration is suggested in patients with coexisting hypertension and renal impairment.

INFORMATION FOR PATIENTS
Patients who receive guanabenz should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

LABORATORY TESTS
In clinical trials, no clinically significant laboratory-test abnormalities were identified during either acute or chronic therapy with guanabenz. Tests carried out included CBC, urinalysis, electrolytes, SGOT, bilirubin, alkaline phosphatase, uric acid, BUN, creatinine, glucose, calcium, phosphorus, total protein, and Coombs' test. During long-term administration of guanabenz, there was a small decrease in serum cholesterol and total triglycerides without any change in the high-density lipoprotein fraction. In rare instances an occasional nonprogressive increase in liver enzymes has been observed. However, no clinical evidence of hepatic disease has been found.

DRUG INTERACTIONS
Guanabenz has not been demonstrated to cause any drug interactions when administered with other drugs, such as digitalis, diuretics, analgesics, anxiolytics, and anti-inflammatory or anti-infective agents, in clinical trials. However, the potential for increased sedation when guanabenz acetate is administered concomitantly with CNS-depressant drugs should be noted.

MAR 30

APPR

DRUG/LABORATORY TEST INTERACTIONS
No laboratory-test abnormalities were identified with the use of guanabenz.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Two-year studies were conducted with oral guanabenz administered in the diet to mice and rats. No evidence of carcinogenic potential was seen in mice given doses of up to 11.5 mg/kg/day (41.4 mg/m²/day) or in rats given doses of up to 9.5 mg/kg/day (83.8 mg/m²/day). On a body-weight basis, these doses are 9X and 7X, respectively, the maximum recommended human daily dose (MRHDD) of 64 mg (based on a 50 kg individual). On a body-surface-area basis, these doses are 1X (mice) and 2X (rats) the MRHDD.

In the Salmonella microsome mutagenicity (Ames) test system, guanabenz at 200 to 500 mcg per plate or at 30 to 50 mcg/mL in suspension gave dose-related increases in the number of mutants in one (TA 1537) of five *Salmonella typhimurium* strains with or without inclusion of rat liver microsomes. No mutagenic activity was seen at doses up to those which inhibit growth in the eukaryotic microorganism, *Schizosaccharomyces pombe*, or in Chinese hamster ovary cells at doses up to those which were lethal to the cells in culture. In another eukaryotic system, *Saccharomyces cerevisiae* guanabenz produced no activity in an assay measuring induction of repairable DNA damage. Reproductive studies showed a decreased pregnancy rate in rats administered high oral doses (9.6 mg/kg) of guanabenz acetate, suggesting an impairment of fertility. The fertility of treated males (9.6 mg/kg) may also have been affected, as suggested by the decreased pregnancy rate of their mates, even though the females received guanabenz only during the last third of pregnancy.

PREGNANCY
Teratogenic Effects: Pregnancy Category C
GUANABENZ ACETATE MAY HAVE ADVERSE EFFECTS ON THE FETUS WHEN ADMINISTERED TO PREGNANT WOMEN. A teratology study in mice has indicated a possible increase in skeletal abnormalities when guanabenz acetate is given orally at doses of 3 to 6 times the maximum recommended human dose of 1 mg/kg. These abnormalities, principally costal and vertebral, were not noted in similar studies in rats and rabbits. However, increased fetal loss has been observed after oral guanabenz acetate administration to pregnant rats (14 mg/kg) and rabbits (20 mg/kg). Reproductive studies of guanabenz in rats have shown slightly decreased live-birth indices, decreased fetal survival rate, and decreased pup body weight at oral doses of 6.4 and 9.6 mg/kg. There are no adequate, well-controlled studies in pregnant women. Guanabenz should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when guanabenz is administered to a nursing woman.

PEDIATRIC USE
The safety and effectiveness of guanabenz in pediatric patients have not been established.

ADVERSE REACTIONS:
The incidence of adverse effects has been ascertained from controlled clinical studies conducted in the United States and is based on data from 859 patients who received guanabenz for up to 3 years. There is some evidence that the side effects are dose-related.

The following table shows the incidence of adverse effects occurring in at least 5% of patients in a study comparing guanabenz acetate to placebo, at a starting dose of 8 mg b.i.d.

Adverse Effect	Placebo (%) n=102	Guanabenz Acetate (%) n=109
Dry mouth	7	28
Drowsiness or sedation	12	39
Dizziness	7	17
Weakness	7	10
Headache	6	5

In other controlled clinical trials at the starting dose of 16 mg/day in 476 patients, the incidence of dry mouth was slightly higher (38%) and that of dizziness was slightly lower (12%), but the incidence of the most frequent adverse effects was similar to the placebo-controlled trial. Although these side effects were not serious, they led to discontinuation of treatment about 15% of the time. In more recent studies using an initial dose of 8 mg/day in 274 patients, the incidence of drowsiness or sedation was lower, about 20%.

Other adverse effects were reported during clinical trials with guanabenz but are not clearly distinguishable from placebo effects and occurred with a frequency of 3% or less:
Cardiovascular - chest pain, edema, arrhythmias, palpitations.
Gastrointestinal - nausea, epigastric pain, diarrhea, vomiting, constipation, abdominal discomfort.
Central nervous system - anxiety, ataxia, depression, sleep disturbances.
ENT disorders - nasal congestion.
Eye disorders - blurring of vision.
Musculoskeletal - aches in extremities, muscle aches.
Respiratory - dyspnea.
Dermatologic - rash, pruritus.
Urogenital - urinary frequency, disturbances of sexual function (decreased libido, impotence).
Other - gynecomastia, taste disorders.
In very rare instances atrioventricular dysfunction, up to and including complete AV block, has been caused by guanabenz.

DRUG ABUSE AND DEPENDENCE:
No reported dependence or abuse has been associated with the administration of guanabenz acetate tablets.

OVERDOSAGE:
Accidental ingestion of guanabenz acetate tablets caused hypotension, somnolence, lethargy, irritability, miosis, and bradycardia in two pediatric patients aged one and three years. Gastric lavage and administration of pressor substances, fluids, and oral activated charcoal resulted in complete and uneventful recovery within 12 hours in both patients.

Since experience with accidental overdosage is limited, the suggested treatment is mainly supportive while the drug is being eliminated from the body and until the patient is no longer symptomatic. Vital signs and fluid balance should be carefully monitored. An adequate airway should be maintained and, if indicated, assisted respiration instituted. There are no data available on the dialyzability of guanabenz.

DOSAGE AND ADMINISTRATION:
Dosage with guanabenz acetate tablets should be individualized. A starting dose of 4 mg twice a day is recommended, whether guanabenz acetate tablets are used alone or with a thiazide diuretic. Dosage may be increased in increments of 4 to 8 mg per day every one to two weeks, depending on the patient's response. The maximum dose studied to date has been 32 mg twice daily, but doses as high as this are rarely needed.

HOW SUPPLIED:
Guanabenz Acetate Tablets, USP are available in the following dosage strengths:

4 mg (guanabenz base), round, unscored, grey, flat, beveled edge tablets, imprinted "E 41" in bottles of 100 and 1000 tablets
8 mg (guanabenz base), round, scored, grey, flat, beveled edge tablets, imprinted "E 42" in bottles of 100 and 1000 tablets.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F).
Protect from moisture.

Dispense in a tight, light-resistant container as defined in the USP/NF.

Protect from light. Keep tightly closed.

Rx only

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Iss. 6/98
MF0041Iss0698

GUANABENZ ACETATE TABLETS, USP

Iss. 0698

GUANABENZ ACETATE TABLETS, USP

MARK

FINAL PRINTED LABEL

Lot No.:
Exp. Date:

USUAL DOSAGE AND COMPLETE PRESCRIBING INFORMATION: See accompanying literature.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 6/98

NDC 0185-0041-01

Guanabenz Acetate Tablets, USP

4 mg*

Rx only

100 Tablets

Eon Labs

*Each tablet contains: Guanabenz acetate equivalent to 4 mg of guanabenz (as the free base).

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

30

N 3 0185-0041-01 5

Lot No.:
Exp. Date:

USUAL DOSAGE AND COMPLETE PRESCRIBING INFORMATION: See accompanying literature.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 6/98

NDC 0185-0041-10

Guanabenz Acetate Tablets, USP

4 mg*

Rx only

1000 Tablets

Eon Labs

*Each tablet contains: Guanabenz acetate equivalent to 4 mg of guanabenz (as the free base).

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

30

N 3 0185-0041-10 7

Lot No.:
Exp. Date:

USUAL DOSAGE AND COMPLETE PRESCRIBING INFORMATION: See accompanying literature.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 6/98

NDC 0185-0042-01

Guanabenz Acetate Tablets, USP

8 mg*

Rx only

100 Tablets

Eon Labs

*Each tablet contains: Guanabenz acetate equivalent to 8 mg of guanabenz (as the free base).

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

30

N 3 0185-0042-01 2

Lot No.:
Exp. Date:

USUAL DOSAGE AND COMPLETE PRESCRIBING INFORMATION: See accompanying literature.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 6/98

NDC 0185-0042-10

Guanabenz Acetate Tablets, USP

8 mg*

Rx only

1000 Tablets

Eon Labs

*Each tablet contains: Guanabenz acetate equivalent to 8 mg of guanabenz (as the free base).

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

30

N 3 0185-0042-10 4