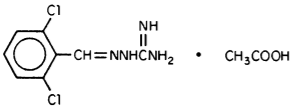




# Wytensin® (guanabenz acetate) Tablets

## Description

Wytensin (guanabenz acetate), an antihypertensive agent for oral administration, is an aminoguanidine derivative, 2,6-dichlorobenzylideneaminoguanidine acetate, and its structural formula is:



It is an odorless, white to off-white, crystalline substance, sparingly soluble in water and soluble in alcohol, with a molecular weight of 291.14. Each tablet of Wytensin is equivalent to 4 mg or 8 mg of free guanabenz base. The inactive ingredients present are cellulose, iron oxide, lactose, and magnesium stearate. The 8 mg dosage strength also contains FD&C Blue 2.

Wytensin is available as 4 mg or 8 mg tablets for oral administration.

## Clinical Pharmacology

Wytensin 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 Wytensin 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 Wytensin is about 6 hours. The site or sites of metabolism of Wytensin have not been determined. The effect of meals on the absorption of Wytensin has not been studied.

## PHARMACODYNAMICS

The onset of the antihypertensive action of Wytensin 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 Wytensin 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. Wytensin 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, Wytensin, 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. Wytensin 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 Wytensin. 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 Wytensin lost one to four pounds of body weight. The mechanism of this weight loss has not been established. Tolerance to the antihypertensive effect of Wytensin has not been observed.

During long-term administration of Wytensin, 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 Wytensin. No changes in serum electrolytes, uric acid, blood urea nitrogen, calcium, or glucose have been observed.

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

## Indication and Usage

Wytensin is indicated in the treatment of hypertension. It may be employed alone or in combination with a thiazide diuretic.

## Contraindication

Wytensin is contraindicated in patients with a known sensitivity to the drug or any of the tablet ingredients.

## Precautions

### GENERAL

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

2. Patients with vascular insufficiency: Wytensin, 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 Wytensin 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 Wytensin is altered in patients with alcohol-induced liver disease. Mean plasma concentrations of Wytensin 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 Wytensin is administered to patients with hypertension and coexisting chronic hepatic dysfunction.

5. Patients with renal impairment: The disposition of orally administered Wytensin is altered modestly in patients with renal impairment. Wytensin'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 Wytensin dose titration is suggested in patients with coexisting hypertension and renal impairment.

## INFORMATION FOR PATIENTS

Patients who receive Wytensin 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 Wytensin. 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 Wytensin, 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

Wytensin 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 Wytensin is administered concomitantly with CNS-depressant drugs should be noted.

## DRUG/LABORATORY TEST INTERACTIONS

No laboratory-test abnormalities were identified with the use of Wytensin.

## CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Two-year studies were conducted with oral Wytensin 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/m<sup>2</sup>/day) or in rats given doses of up to 9.5 mg/kg/day (83.8 mg/m<sup>2</sup>/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.

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(guanabenz acetate)  
**Tablets**  
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In the Salmonella microsome mutagenicity (Ames) test system, Wytensin® 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*, Wytensin 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 Wytensin, 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 Wytensin only during the last third of pregnancy.

## PREGNANCY

### Pregnancy Category C

WYTENSIN 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 Wytensin is given orally at doses of 3 to 6 times the maximum recommended human dose of 1.0 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 Wytensin administration to pregnant rats (14 mg/kg) and rabbits (20 mg/kg). Reproductive studies of Wytensin 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. Wytensin 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 Wytensin is administered to a nursing woman.

## PEDIATRIC USE

The safety and effectiveness of Wytensin 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 Wytensin 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 Wytensin to placebo, at a starting dose of 8 mg b.i.d.

Adverse Effect	Placebo (%) n=102	Wytensin (%) 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 Wytensin 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 Wytensin.

## Drug Abuse and Dependence

No reported dependence or abuse has been associated with the administration of Wytensin.

## Overdosage

Accidental ingestion of Wytensin 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 Wytensin.

## Dosage and Administration

Dosage with Wytensin should be individualized. A starting dose of 4 mg twice a day is recommended, whether Wytensin is 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

Wytensin® (guanabenz acetate) Tablets are available in the following dosage strengths:

4 mg, orange, five-sided tablet with a raised "W" and a "4" under the "W" on one side and "WYETH 73" on reverse side, in bottles of 100 tablets (NDC 0008-0073-01) and 500 tablets (NDC 0008-0073-04) and in Redipak® cartons of 100 tablets (10 blister strips of 10 – NDC 0008-0073-05).

8 mg, gray, five-sided tablet with a raised "W" and an "8" under the "W" on one side and "WYETH 74" on scored reverse side, in bottles of 100 tablets (NDC 0008-0074-01).

The appearance of these tablets is a trademark of Wyeth-Ayerst Laboratories.

## Keep tightly closed

## Store at room temperature, approximately 25° C (77° F)

## Protect from light

## Dispense in a light-resistant, tight container