



Cytadren[®] Tablets

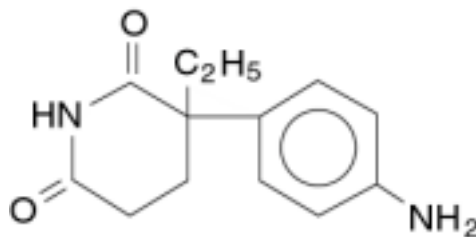
aminoglutethimide tablets USP

Rx only

Prescribing Information

DESCRIPTION

Cytadren, aminoglutethimide tablets USP, is an inhibitor of adrenocortical steroid synthesis, available as 250-mg tablets for oral administration. Its chemical name is 3-(4-aminophenyl)-3-ethyl-2,6-piperidinedione, and its structural formula is



Aminoglutethimide USP is a fine, white or creamy white, crystalline powder. It is very slightly soluble in water, and readily soluble in most organic solvents. It forms water-soluble salts with strong acids. Its molecular weight is 232.28.

Inactive Ingredients. Cellulose compounds, colloidal silicon dioxide, starch, stearic acid, and talc.

CLINICAL PHARMACOLOGY

Cytadren inhibits the enzymatic conversion of cholesterol to Δ^5 -pregnenolone, resulting in a decrease in the production of adrenal glucocorticoids, mineralocorticoids, estrogens, and androgens.

Cytadren blocks several other steps in steroid synthesis, including the C-11, C-18, and C-21 hydroxylations and the hydroxylations required for the aromatization of androgens to estrogens, mediated through the binding of Cytadren to cytochrome P-450 complexes.

A decrease in adrenal secretion of cortisol is followed by an increased secretion of pituitary adrenocorticotrophic hormone (ACTH), which will overcome the blockade of adrenocortical steroid synthesis by Cytadren. The compensatory increase in ACTH secretion can be suppressed by the simultaneous administration of hydrocortisone. Since Cytadren

increases the rate of metabolism of dexamethasone but not that of hydrocortisone, the latter is preferred as the adrenal glucocorticoid replacement.

Although Cytadren inhibits the synthesis of thyroxine by the thyroid gland, the compensatory increase in thyroid-stimulating hormone (TSH) is frequently of sufficient magnitude to overcome the inhibition of thyroid synthesis due to Cytadren. In spite of an increase in TSH, Cytadren has not been associated with increased prolactin secretion.

Note: Cytadren was marketed previously as an anticonvulsant but was withdrawn from marketing for that indication in 1966 because of the effects on the adrenal gland.

Pharmacokinetics

Cytadren is rapidly and completely absorbed after oral administration. In 6 healthy male volunteers, maximum plasma levels of Cytadren averaged 5.9 µg/mL at a median of 1.5 hours after ingestion of two 250-mg tablets. The bioavailability of tablets is equivalent to equal doses given as a solution. After ingestion of a single oral dose, 34%-54% is excreted in the urine as unchanged drug during the first 48 hours, and an additional fraction as the N-acetyl derivative.

The half-life of Cytadren in normal volunteers given single oral doses averaged 12.5 ± 1.6 hours.

Upon withdrawal of therapy with Cytadren, the ability of the adrenal glands to synthesize steroid returns, usually within 72 hours.

INDICATIONS AND USAGE

Cytadren is indicated for the suppression of adrenal function in selected patients with Cushing's syndrome. Morning levels of plasma cortisol in patients with adrenal carcinoma and ectopic ACTH-producing tumors were reduced on the average to about one half of the pretreatment levels, and in patients with adrenal hyperplasia to about two thirds of the pretreatment levels, during 1-3 months of therapy with Cytadren. Data available from the few patients with adrenal adenoma suggest similar reductions in plasma cortisol levels. Measurements of plasma cortisol showed reductions to at least 50% of baseline or to normal levels in one third or more of the patients studied, depending on diagnostic groups and time of measurement.

Because Cytadren does not affect the underlying disease process, it is used primarily as an interim measure until more definitive therapy such as surgery can be undertaken or in cases where such therapy is not appropriate. Only small numbers of patients have been treated for longer than 3 months. A decreased effect or "escape phenomenon" seems to occur more frequently in patients with pituitary-dependent Cushing's syndrome, probably because of increasing ACTH levels in response to decreasing glucocorticoid levels.

Cytadren should be used only in those patients who are responsive to treatment.

CONTRAINDICATIONS

Cytadren is contraindicated in those patients with serious forms, and/or more severe manifestations, of hypersensitivity to glutethimide or aminoglutethimide.

WARNINGS

Cytadren may cause adrenocortical hypofunction, especially under conditions of stress, such as surgery, trauma, or acute illness. Patients should be carefully monitored and given hydrocortisone and mineralocorticoid supplements as indicated. Dexamethasone should not be used. (See PRECAUTIONS, Drug Interactions.)

Cytadren also may suppress aldosterone production by the adrenal cortex and may cause orthostatic or persistent hypotension. The blood pressure should be monitored in all patients at appropriate intervals. Patients should be advised of the possible occurrence of weakness and dizziness as symptoms of hypotension, and of measures to be taken should they occur.

The effects of Cytadren may be potentiated if it is taken in combination with alcohol.

Cytadren can cause fetal harm when administered to a pregnant woman. In the earlier experience with the drug in about 5000 patients, two cases of pseudohermaphroditism were reported in female infants whose mothers were treated with Cytadren and concomitant anticonvulsants. Normal pregnancies have also occurred in patients treated with Cytadren.

When administered to rats at doses 1/2 and 1 1/4 times the maximum daily human dose, Cytadren caused a decrease in fetal implantation, an increase in fetal deaths, and a variety of teratogenic effects. The compound also caused pseudohermaphroditism in rats treated with approximately 3 times the maximum daily human dose. If this drug must be used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General

This drug should be administered only by physicians familiar with its use and hazards. Therapy should be initiated in a hospital. (See DOSAGE AND ADMINISTRATION.)

Information for Patients

Patients should be warned that drowsiness may occur and that they should not drive, operate potentially dangerous machinery, or engage in other activities that may become hazardous because of decreased alertness.

Patients should also be warned of the possibility of hypotension and its symptoms (see WARNINGS).

Laboratory Tests

Hypothyroidism may occur in association with Cytadren; hence, appropriate clinical observations should be made and laboratory studies of thyroid function performed as indicated. Supplementary thyroid hormone may be required.

Hematologic abnormalities in patients receiving Cytadren have been reported (see ADVERSE REACTIONS). Therefore, baseline hematologic studies should be performed, followed by periodic hematologic evaluation.

Since elevations in SGOT, alkaline phosphatase, and bilirubin have been reported, appropriate clinical observations and regular laboratory studies should be performed before and during therapy.

Serum electrolyte levels should be determined periodically.

Drug Interactions

Cytadren accelerates the metabolism of dexamethasone; therefore, if glucocorticoid replacement is needed, hydrocortisone should be prescribed.

Aminoglutethimide diminishes the effect of coumarin and warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study of Cytadren conducted in rats at doses of 10-60 mg/kg/day (approximately 0.04 to 0.2 times the maximum daily therapeutic dose based on surface area, mg/m²) revealed a highly statistically significant dose-related trend in the incidence of benign and malignant neoplasms of the adrenal cortex and thyroid follicular cells in both sexes. A borderline statistically significant increase (0.05 level) in ovarian tubular adenomas was observed at 60 mg/kg/day. Urinary bladder papillomas also showed a statistically significant dose-related trend in males.

Cytadren affects fertility in female rats (see WARNINGS). The relevance of these findings to humans is not known.

Pregnancy Category D

See WARNINGS.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Cytadren, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (see CLINICAL STUDIES IN CHILDREN).

ADVERSE REACTIONS

Untoward effects have been reported in about 2 out of 3 patients with Cushing's syndrome who were treated for 4 or more weeks with Cytadren as the only adrenocortical suppressant.

The most frequent and reversible side effects were drowsiness (approximately 1 in 3 patients), morbilliform skin rash (1 in 6 patients), nausea and anorexia (each approximately 1 in 8 patients), and dizziness (about 1 in 20 patients). The dizziness was possibly caused by lowered vascular resistance or orthostasis. These reactions often disappear spontaneously with continued therapy.

Other Effects Observed

Hematologic: Single instances of neutropenia, leukopenia (patient received concomitant *o,p'*-DDD), pancytopenia (patient received concomitant 5-fluorouracil), and agranulocytosis occurred in 4 of 27 patients with Cushing's syndrome caused by adrenal carcinoma who were treated for at least 4 weeks. In 1 patient with adrenal hyperplasia, hemoglobin levels and hematocrit decreased during the course of treatment with Cytadren. From the earlier experience with the drug used as an anticonvulsant in 1,214 patients, transient leukopenia was the only hematologic effect and was reported once; Coombs'-negative hemolytic anemia also occurred once. In approximately 300 patients with nonadrenal malignancy, 1 in 25 showed some degree of anemia, and 1 in 150 developed pancytopenia during treatment with Cytadren.

Endocrine: Adrenal insufficiency occurred in about 1 in 30 patients with Cushing's syndrome who were treated with Cytadren for 4 or more weeks. This insufficiency tended to involve glucocorticoids as well as mineralocorticoids. Hypothyroidism is occasionally associated with thyroid enlargement and may be detected or confirmed by measuring plasma levels of the thyroid hormone. Masculinization and hirsutism have occasionally occurred in females, as has precocious sexual development in males.

Central Nervous System: Headache was reported in about 1 in 20 patients.

Cardiovascular: Hypotension, occasionally orthostatic, occurred in 1 in 30 patients receiving Cytadren. Tachycardia occurred in 1 in 40 patients.

Gastrointestinal and Liver: Vomiting occurred in 1 in 30 patients. Isolated instances of abnormal findings on liver function tests were reported. Suspected hepatotoxicity occurred in less than 1 in 1000 patients.

Skin: In addition to rash (1 in 6 patients, and often reversible with continued therapy), pruritus was reported in 1 in 20 patients. These may be allergic or hypersensitive reactions. Urticaria has occurred rarely.

Miscellaneous: Fever was reported in several patients who were treated with Cytadren for less than 4 weeks; some of these patients also received other drugs. Myalgia occurred in 1 in 30 patients. Pulmonary hypersensitivity, including allergic alveolitis and interstitial alveolar infiltrates, has occurred rarely.

OVERDOSAGE

Acute Toxicity

No deaths due to overdosage with Cytadren have been reported.

The highest known doses that have been survived are 7 g (33-year-old woman), 7.5-10 g (16-year-old girl), and 10 g (10-year-old boy).

Oral LD₅₀'s (mg/kg): rats, 1800; dogs, >100. Intravenous LD₅₀'s (mg/kg): rats, 156; dogs, >100.

Signs and Symptoms

An acute overdose with Cytadren may reduce the production of steroids in the adrenal cortex to a degree that is clinically relevant. The following manifestations may be expected:

Respiratory Function: Respiratory depression, hypoventilation.

Cardiovascular System: Hypotension, hypovolemic shock due to dehydration.

Central Nervous System/Muscles: Somnolence, lethargy, coma, ataxia, dizziness, fatigue. (Extreme weakness has been reported with divided doses of 3 g daily.)

Gastrointestinal System: Nausea, vomiting.

Renal Function: Loss of sodium and water.

Laboratory Findings: Hyponatremia, hypochloremia, hyperkalemia, hypoglycemia.

The signs and symptoms of acute overdosage with Cytadren may be aggravated or modified if alcohol, hypnotics, tranquilizers, or tricyclic antidepressants have been taken at the same time.

Treatment

Symptomatic treatment of overdosage is recommended.

Since aminoglutethimide and glutethimide are chemically related, measures that have been used in successfully removing glutethimide from the body might be useful in removing aminoglutethimide.

Gastric lavage and unspecified supportive treatment have been employed. Full consciousness following deep coma was regained 40 hours or less after ingestion of 3 or 4 g without lavage. No evidence of hematologic, renal, or hepatic effects was subsequently found.

Close monitoring should be provided, and appropriate measures taken to support vital functions, if necessary.

If deficiency of circulating glucocorticoid develops, an intravenous infusion of a soluble hydrocortisone preparation (100 mg of hydrocortisone sodium succinate in 500 mL of isotonic sodium chloride solution) and 50 mL of 40% glucose solution should be given within 3 hours. After the initial infusion is completed, an intravenous administration of

hydrocortisone, 10 mg per hour, should be continued until the patient is able to take oral cortisone.

If hypovolemia or hypotension occurs, an intravenous administration of norepinephrine, 10 mg, in 500 mL of isotonic sodium chloride should be administered according to the patient's needs and response. After rehydration, 500 mL of plasma or blood should be given for maintenance of sufficient circulatory volume.

Dialysis may be considered in severe intoxication.

DOSAGE AND ADMINISTRATION

Adults

Treatment should be instituted in a hospital until a stable dosage regimen is achieved. Therapy should be initiated with 250 mg orally four times daily, preferably at 6-hour intervals. Adrenocortical response should be followed by careful monitoring of plasma cortisol levels until the desired level of suppression is achieved. If the level of cortisol suppression is inadequate, the dosage may be increased in increments of 250 mg daily at intervals of 1-2 weeks to a total daily dose of 2 g. Dose reduction or temporary discontinuation of therapy may be required in the event of adverse effects, including extreme drowsiness, severe skin rash, or excessively low cortisol levels. If a skin rash persists for longer than 5-8 days or becomes severe, the drug should be discontinued. It may be possible to reinstate therapy at a lower dosage following the disappearance of a mild or moderate rash. Mineralocorticoid replacement (e.g., fludrocortisone) may be necessary. If glucocorticoid replacement therapy is needed, 20-30 mg of hydrocortisone orally in the morning will replace endogenous secretion.

HOW SUPPLIED

Tablets 250 mg — white, round, scored into quarters (imprinted CIBA 24)

Bottles of 100 NDC 0083-0024-30

Protect from light.

Do not store above 30°C (86°F).

Dispense in tight, light-resistant container (USP).

CLINICAL STUDIES IN CHILDREN

Clinical investigations included 9 patients aged 2 1/2 to 16 years; 4 of these were aged 10 or less. Seven of the patients received other therapies (drugs or irradiation) either with Cytadren or within a short period before initiation of therapy with Cytadren. Diagnoses included 5 patients with adrenal carcinoma, 3 with adrenal hyperplasia, and 1 with ectopic ACTH-producing tumor. Duration of treatment ranged from 3 days to 6 1/2 months. Dosages ranged from 0.375 g to 1.5 g daily. In general, smaller doses were used for younger patients; for example, a 2 1/2-year-old received 0.5-0.75 g daily, a 3 1/2-year-old received 0.5 g daily, and all others over 10 years of age received 0.75-1.5 g daily. Results are difficult

to evaluate because of the concomitant therapy, duration of therapy, or inadequate laboratory documentation. Most patients did show decreases in plasma or urinary steroids at some time during treatment, but these may have been due to other therapeutic modalities or their combinations.

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