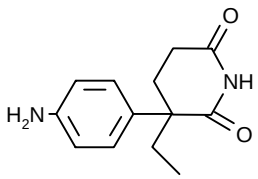
CYTADREN®

NAME OF THE DRUG

Aminoglutethimide

DESCRIPTION

Cytadren is supplied as 250 mg tablets of aminoglutethimide for oral administration. The active ingredient is 2-(p-aminophenyl)-2-ethylglutarimide. The structural formula is:



The form of aminoglutethimide used clinically is a racemic mixture of d-and l-enantiomers of which the d- form possesses the major steroid inhibitory property in the adrenal cortex and aromatase enzyme blocking activity in the extra-adrenal tissues (e.g. liver, muscles, fat, breast tumour tissue, etc).

Empirical formula is C_{13} H_{16} N_2 O_2. Molecular weight: 232.27
Melting point: 152°C. It is very slightly soluble in water but is readily soluble in most organic solvents.

Excipients: silica-colloidal anhydrous, hypromellose, magnesium stearate, starch-maize, talc-purified.

PHARMACOLOGY

Pharmacodynamics

Breast cancer:

Aminoglutethimide, the active substance of Cytadren, inhibits the enzyme aromatase which converts androgens to oestrogens. Aromatase is present in a number of tissues, including ovary, adipose tissue, muscle, liver and breast cancer tissue. In premenopausal women, the primary source of circulating oestrogens is the ovary, whilst in postmenopausal women oestrogens are derived primarily from extra-glandular (non-ovarian) aromatisation of adrenal precursors. Inhibition of aromatase leads to a reduction in oestrogen biosynthesis in both pre- and postmenopausal women. However, in premenopausal women the reduction in ovarian synthesis can be overcome by a compensatory increase in gonadotrophins.

Oestrogens are important in maintaining the growth of hormone-dependent breast cancer. Treatment designed to reduce circulating concentrations of oestrogens results in tumour regression in patients with oestrogen receptor-positive tumours. Inhibition of aromatase by Cytadren suppresses oestrogen biosynthesis in peripheral tissues and in the breast cancer tissue itself. Clinical experience with Cytadren shows that it is an effective treatment for advanced breast cancer in postmenopausal women.

Studies on postmenopausal women with metastatic breast carcinoma indicate that objective responses to Cytadren therapy may be seen in approximately one third of unselected patients. The median duration of response is similar to that resulting from surgical adrenalectomy. Preliminary data from 2 studies in postmenopausal women with positive oestrogen receptor status indicated an objective response ranging from 50 to 68%. These data indicate that a high proportion of patients selected on the basis of oestrogen receptor levels should be expected to respond to Cytadren-hydrocortisone treatment. Patients with metastases in soft tissue and bone show the highest response rates to Cytadren. Some patients experience marked subjective relief from bone pain. Some studies have shown that 250 mg twice daily has similar efficacy to a 1000 mg/day dosage regimen.

A proportion (varying in different trials up to 30%) of patients who do not respond to tamoxifen, respond subsequently to Cytadren, whereas the reverse does not appear to be the case. About two-thirds of patients who relapsed after an initial response to tamoxifen responded subsequently to Cytadren. Because of this possible subsequential efficacy and the higher incidence of adverse reactions with Cytadren, it has been recommended as second-line hormonal therapy (see "DOSAGE and ADMINISTRATION") in the treatment of metastatic breast cancer. Simultaneous combination of two hormonal treatments has not been found to increase the response rate.

Cushing's syndrome:
The inhibitory effect of Cytadren is brought about by competitive binding to cytochrome P450. Cytadren inhibits several cytochrome-P450-mediated steps in the hydroxylation of the steroids in the adrenal cortex, including the enzymatic conversion of cholesterol to pregnenolone. Cytadren thus reduces the production of glucocorticoids and mineralocorticoids from the adrenal cortex, and reduces excessive plasma cortisol in patients with adrenocortical hyperfunction, such as Cushing's syndrome (secondary to adrenal steroid-producing tumours or ACTH- producing tumours).

Plasma cortisol levels (morning) in patients with adrenal carcinoma and ectopic ACTH-producing tumours may be reduced to about one-half the pretreatment levels, and in patients with adrenal hyperplasia to about two-thirds of the pre-treatment levels during one to three months' treatment with Cytadren. Data from a few patients with adrenal adenoma suggest that similar reductions in plasma cortisol levels may be achieved. Measurements of plasma cortisol showed reductions to at least 50% of baseline or to normal levels in one-third or more of patients studied, depending on diagnostic groups and time of measurement.

Because Cytadren treatment does not affect the underlying disease process related to Cushing's syndrome, it has been used primarily during clinical investigations either as an interim measure until more definite therapy such as surgery can be undertaken, in cases where such therapy is not appropriate, or while the full effects of pituitary irradiation are awaited. Only small numbers of patients have been treated for longer than 3 months. A decreased effect or escape from a favourable effect seems to occur more frequently in pituitary-dependent Cushing's syndrome, probably because of increasing ACTH levels in response to decreasing glucocorticoid levels.

Other effects:
A fall in adrenal secretion of cortisol leads to a reflex rise in adrenocorticotrophic hormone (ACTH) which will overcome the cortisol-lowering effect of Cytadren. This compensatory increase in ACTH secretion can be suppressed by the simultaneous administration of a glucocorticoid (see "DOSAGE and ADMINISTRATION").

The effect of aminoglutethimide on the adrenal gland is reversible. After cessation of 5 years' aminoglutethimide-hydrocortisone treatment in 5 patients, cortisol levels returned to normal levels within 18 hours and cortisol response to stress normalised by 36 hours. These data suggest that adrenal recovery after aminoglutethimide-hydrocortisone administration is rapid and that these drugs can safely be stopped abruptly even after prolonged treatment.

Cytadren inhibits the synthesis of thyroxine by the thyroid gland. There is, however, a compensatory increase in thyroid stimulating hormone (TSH) secretion which is usually of sufficient magnitude to overcome this blockade. Thyroxine replacement therapy is therefore only occasionally required. Thyroid function should be monitored (see "PRECAUTIONS" and "Patient Monitoring").

In spite of an increase in TSH, Cytadren has not been associated with increased prolactin secretion.

Pharmacokinetics

Absorption:
Cytadren is rapidly absorbed after oral administration and its systemic availability is estimated to be 92-98%. The bioavailability of Cytadren administered as tablets is equivalent to that of an oral solution. There are no data on the absolute bioavailability of aminoglutethimide, that is, compared with the same dose given intravenously. The peak plasma concentrations of aminoglutethimide are reached within 1-4 hours after oral administration of a 500mg dose and average 5.9 microgram/mL. Mean steady-state plasma concentrations in patients receiving 500mg and 1000 mg aminoglutethimide daily are variable and are approximately 4.5 microgram/mL and 9.5 microgram/mL, respectively, after 3 months therapy. For doses ranging from 125 to 1000 mg per day, steady-state concentrations are proportional to dose.

Distribution:
The concentration of aminoglutethimide in blood cells is 1.4 to 1.7 times that in plasma. The extent of binding to plasma proteins is 21 to 25%, with the major binding protein being albumin. Total plasma clearance averages 3.5 L/h following single aminoglutethimide doses. It increases to 4.4 L/h during long-term treatment of patients, owing to hepatic enzyme induction. At the same time the volume of distribution decreases from 76 to 53 L.

Metabolism:
Aminoglutethimide is partly cleared from the body by hepatic metabolism and partly by direct renal excretion. Metabolism primarily involves oxidation and acylation of the aromatic amino group of the drug. The metabolites formed have no inhibitory effect on aromatase and desmolase, or are several times less active than aminoglutethimide. The major circulating metabolite in plasma, N-acetylaminoglutethimide, reaches steady-state plasma concentrations of approximately 25-35% of those of the unchanged drug.

Excretion:
In a study of patients with advanced breast cancer, the plasma elimination half-life after a single dose of aminoglutethimide was 15.5 ± 4.3 hours (mean ± SD). As a result of changes in total plasma clearance and volume of distribution, the plasma elimination half-life fell to 8.9 ± 2.4 hours at steady-state. This finding was supported by another study in which plasma elimination half-life fell from 10.1 ± 1.7 hours (mean ± SD) after a single dose to 6.9 ± 1.2 hours after 8 weeks of treatment.

Excretion of aminoglutethimide and its metabolites is predominantly renal: 90 to 97% of a dose is recovered in urine, and only 3 to 7% in bile. Urinary output of unchanged aminoglutethimide accounts for about 47% of a dose at steady state. N-Hydroxyl-aminoglutethimide is the major urinary metabolite in patients whose liver enzymes have been induced by the drug, constituting 20 to 25% of a dose on average. N-Acetyl-aminoglutethimide is a minor product in urine, accounting for less than 5% of the dose at steady-state. The actual yield of this metabolite depends on the phenotype: it is about 4% in fast acetylators and 2% in slow acetylators. Thus, acetylation is an unimportant pathway of drug clearance in either case.

Effect of disease on pharmacokinetics:
Possible effects of liver or kidney dysfunction on the disposition of aminoglutethimide have not been specifically investigated. However, retention of aminoglutethimide due to insufficient metabolism or excretion has not been reported so far.

INDICATIONS

Metastatic Breast Carcinoma

Cytadren in combination with adrenocorticoid replacement is indicated for the treatment of metastatic breast carcinoma occurring in postmenopausal, including oophorectomised, women and in male patients.

Cushing's Syndrome

Cytadren is indicated for the suppression of adrenal cortical function in selected adult patients with Cushing's syndrome.

CONTRAINDICATIONS

Cytadren is contraindicated in patients with hypersensitivity to glutethimide or amino-glutethimide, and in patients with inducible porphyria or in pregnancy (see "PRECAUTIONS").

PRECAUTIONS

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").

Use with Caution in the Following Circumstances

Cytadren may cause adrenal cortical hypofunction, especially under conditions of stress such as surgery, trauma, or acute illness. Patients should be carefully monitored and given hydrocortisone as indicated. Dexamethasone should not be used (see "Interactions with Other Drugs"). If inhibition of aldosterone synthesis leads to hyponatraemia, hypotension, or dizziness, a mineralocorticoid (e.g. fludrocortisone acetate 0.1 mg daily or on alternate days) should be given in addition (see "DOSAGE AND ADMINISTRATION" and "Patient Monitoring"). 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 most common side-effects of Cytadren (drowsiness and lethargy) are commonly observed at the beginning of treatment and generally abate after about 6 weeks. They can be considerably alleviated if therapy is begun with a low dosage and increased gradually (see "DOSAGE AND ADMINISTRATION"). Patients should be warned that drowsiness and ataxia may occur and that in its presence they should take care as pedestrians, and not drive, operate potentially dangerous machinery, or engage in other activities with possibly harmful effects.

Patients should also be warned that an extensive itchy rash may occur. In about 15 to 20% of cases a generalised maculopapular urticarial rash, often associated with fever occurs. It

commonly appears after 8 to 10 days and subsides 5 to 8 days later. The symptoms are usually not severe enough to necessitate cessation of therapy but reduction of dose may be required. If the rash does not disappear within 10 days, Cytadren should be temporarily withdrawn and/or the corticosteroid dosage increased.

Isolated cases of allergic alveolitis (eosinophilic pulmonary infiltrates) have been reported. Where such conditions are suspected, Cytadren should be withdrawn immediately. Alveolar haemorrhage was reported in one case.

Haematological abnormalities in patients receiving Cytadren have been reported (see "ADVERSE REACTIONS" and "Patient Monitoring").

Hypothyroidism may occur in association with the use of Cytadren (see "ADVERSE REACTIONS" and "Patient Monitoring").

Use in Special Patient Groups

Children:

The safety and effectiveness of Cytadren for use in children have not been established.

Elderly patients:

There is no evidence to suggest that the dosage should be different in elderly patients unless renal function is impaired.

Renal disease:

As Cytadren is partly excreted unchanged through the kidney, patients with impaired renal function may require a lower dose and should be monitored closely.

Porphyria:

The related drug, glutethimide, has been shown experimentally to have porphyrogenic potential. It is not known whether or not Cytadren has similar potential and, if so, if this is of clinical significance. However, the use of Cytadren should be regarded as contraindicated in patients with a history of inducible porphyria.

Carcinogenicity / Mutagenicity

In a 24 month carcinogenicity study, male and female rats were given 10, 30 or 60 mg/kg aminoglutethimide in the diet (approximately 0.04 to 0.24 times the daily human maximum therapeutic dose based on surface area; mg/m^2). A dose-related increase in the incidence of benign and malignant neoplasms of the adrenal cortex and the thyroid gland was noted for males and females.

No mutagenic potential was evident for aminoglutethimide, as assessed by the Ames test in vitro in histidine auxotrophic strains of Salmonella typhimurium and, in vivo, in a test for

sister chromatid exchange in bone marrow cells and in the nucleus anomaly test in somatic interphase nuclei of Chinese hamsters.

Use In Pregnancy (Category D)

Treatment of male and female rats with aminoglutethimide at doses of 20 and 50 mg/kg (approximately 0.08 to 0.2 times the human daily maximum therapeutic dose based on surface area; mg/m^2) prior to mating caused a decrease in fertility. In a reproduction study, where female rats were treated for 14 days prior to mating and then until Day 21 post partum, doses of 20 and 50 mg/kg p.o. increased the incidence of fetal death and resorption. An increase in fetal resorptions and fetal death was also observed at doses of 5 and 15 mg/kg/day in a peri- and post-natal study in rats.

In rats receiving aminoglutethimide at daily oral doses of 20 and 50 mg/kg/day from Day 6 to Day 15 of gestation, embryotoxicity was observed. Examination of the fetal viscera revealed abnormalities of the genitourinary system (e.g., agenesis of the kidney, dilated ureter, absence of the renal papillae, hypoplastic testis, and cryptorchidism). The frequency of skeletal abnormalities was also significantly increased in fetuses derived from dams treated with high doses of aminoglutethimide.

Since there have been occurrences of pseudohermaphroditism in the newborn infants of women treated with Cytadren during their pregnancy, the possibility of pregnancy should be excluded before prescribing Cytadren for women of child-bearing age. During the treatment such women should employ non-hormonal contraceptives.

Use In Lactation

It is not known if Cytadren is excreted in breast milk, nor is it known if it has a harmful effect on the newborn. Therefore, no recommendations can be made regarding its use in nursing mothers.

Interactions with Other Drugs

By inducing hepatic enzymes, Cytadren increases its own metabolism and also that of several drugs including synthetic glucocorticoids such as dexamethasone, warfarin and other oral anti-coagulants, digitoxin, theophylline, medroxyprogesterone and oral antidiabetics. Therefore, appropriate laboratory tests must be performed and, if necessary, the dosage of these drugs may have to be raised.

Concomitant therapy with diuretics may lead to hyponatraemia.

The adverse effects of Cytadren may be potentiated if it is taken in combination with alcohol (see "ADVERSE REACTIONS").

ADVERSE REACTIONS

The adverse reactions below are listed according to the following frequency values:

	Frequency (%)
Very common	≥ 10%
Common (frequent)	≥ 1% and < 10%
Uncommon (infrequent)	≥ 0.1% and < 1%
Rare	≥ 0.01% and < 0.1%
Very rare	< 0.01%

Central nervous system:
Very common: drowsiness, lethargy.
Common: ataxia, dizziness (vertigo).
Rare: headache, depression, confusion.
Very rare: insomnia.

Skin:
Very common: rash (morbilliform and/or maculopapular), sometimes accompanied by fever.
Rare: pruritus, urticaria.
Very rare: exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome

Gastrointestinal system:
Very common: nausea.
Common: vomiting.
Rare: diarrhoea, constipation, anorexia.

Systemic:
Common: fever.
Rare: sweating.

Liver:
Very rare: jaundice (cholestatic type, associated with itching and skin rash).

Endocrine system:
Rare: adrenal insufficiency (hyponatraemia, hypotension, dizziness, hypoglycaemia). Rarely, adrenal haematomas have been seen at surgery in patients receiving aminoglutethimide. Cellular hypertrophy, cytoplasmic vacuolization, and excessive accumulation of lipids have been observed in adrenal tissue.
Very rare: hypothyroidism, inappropriate ADH secretion, masculinisation and hirsutism in females.

Kidney:
Very rare: renal function abnormalities.

Cardiovascular system:
Rare: hypotension.

Haematological system:
Rare: agranulocytosis, leukopenia, thrombocytopenia.
Very rare: pancytopenia, anaemia.

Allergy:
Very rare: allergic/anaphylactic reactions, allergic alveolitis (eosinophilic pulmonary infiltrates), alveolar haemorrhage.

Laboratory abnormalities:
Rare: increased bilirubin and elevation of alkaline phosphatase and AST (SGOT); increased gamma-glutamyl transferase (gamma-GT) due to the enzyme-inducing effect of Cytadren and usually not a sign of liver damage; hyponatraemia; hyperkalaemia.
Very rare: hypercholesterolaemia; decreased thyroxine level accompanied by increased TSH.

Adverse reactions due to glucocorticoid replacement therapy:
Very rare: Cushingoid symptoms (moon face, weight gain, oedema), hyperadrenalism, hypercalcaemia, arterial hypertension, muscle cramps, hyperglycaemia.

Adverse reactions due to mineralocorticoid replacement therapy:
Very rare: hypertension and congestive heart failure due to a marked effect on sodium retention.

The adverse reactions below may not necessarily be ascribed to Cytadren therapy. They are listed as alerting information:
nystagmus, unstable gait, weakness, anxiety, hallucinations, numbness, shortness of breath, systemic lupus erthematosus, Coombs' negative haemolytic anaemia, emotional lability, poor memory, depersonalisation, motor disturbances, palsy or tremor, incoherence, nervousness, seizures, dry skin, abdominal discomfort, indigestion, serum sickness, ascites, fatigue, heat intolerance, chills, arthralgia, visual or hearing disturbances and urinary retention.

DOSAGE AND ADMINISTRATION

It is recommended that therapy be initiated in a hospital in order to facilitate correct titration of dosage.

Tolerability can be improved by administering the drug in small, gradually increasing doses (e.g. by starting the medication with a dosage of 125mg twice daily).

Metastatic Breast Carcinoma

Cytadren is currently considered second-line hormonal therapy in postmenopausal patients with metastatic breast cancer who have not responded to tamoxifen or who have relapsed after an initial response.

The usual dose of Cytadren in metastatic breast cancer is 250mg every 6 hours. Patients receive 250mg Cytadren twice daily for the first week; 250mg three times daily for the second week; thereafter 250mg four times daily. The gradual initiation of therapy is advisable to minimise side effects. Therapeutic responses have been reported from 500 mg daily.

Treatment with Cytadren should be continued for at least 6 weeks before assessment of efficacy can be made.

Hydrocortisone in daily doses of 40mg, preferably 10mg in the morning, 10mg in the evening and 20mg at bedtime, is recommended as an adrenocortical replacement since its metabolism is not altered in the presence of Cytadren. In addition, administration of a mineralocorticoid such as fludrocortisone acetate (0.1 mg/day or on alternate days) may be necessary to prevent or reduce symptoms of mineralocorticoid insufficiency.

Cushing's Syndrome

Adults: Treatment should be instituted in a hospital until a stable dosage regimen is achieved. Therapy should be adjusted initially to 250mg orally four times daily, preferably at 6 hour intervals. Adrenal cortical response should be monitored carefully by estimations of plasma cortisol until the desired level of suppression is achieved. If cortisol suppression is inadequate, the dosage may be increased in increments of 250mg daily at intervals of one or two weeks to a total daily dose of 2 grams.

Mineralocorticoid replacement therapy (e.g. fludrocortisone acetate) may be necessary. If glucocorticoid therapy is needed, 20 to 30 mg of hydrocortisone orally in the morning will replace endogenous secretion.

Patient Monitoring

Dose reduction or temporary discontinuation may be required in the event of adverse reactions; for example - extreme drowsiness, severe rash, disabling ataxia or excessively low cortisol levels. If a rash persists for longer than five to eight 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 to moderate rash.

During treatment with Cytadren, the following checks should be carried out:
Cytadren may suppress production of aldosterone by the adrenal cortex which may result in orthostatic or persistent hypotension. The blood pressure should be monitored in all patients at appropriate intervals. Adrenal suppression may be monitored by plasma DHEA-S or oestrone levels as plasma cortisol levels will be altered by exogenous steroids.

Hypothyroidism may occur in association with the use of Cytadren. Hence, appropriate clinical observations should be made and laboratory studies of thyroid function performed every 3 months during therapy. Supplementary thyroid hormone may be required. In the event of hypothyroidism, substitution therapy with thyroxine must be instituted; such therapy, however, very seldom proves necessary because the decrease in thyroxine provoked by Cytadren is usually offset by a reactive rise in TSH.

Haematological tests should be performed before starting treatment and at regular intervals thereafter. During the first 2 to 3 months of treatment, blood counts are indicated once every 2 weeks. If blood dyscrasias develop, Cytadren should be withdrawn.

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

Serum electrolytes should be determined periodically and a small dose of mineralocorticoid (e.g. 0.1 mg fludrocortisone acetate) administered if indicated by clinical or electrolyte status.

OVERDOSAGE

Signs and symptoms:
Following an overdose of Cytadren, signs and symptoms may appear which are the result of its effects both on the adrenal cortex and on the central nervous system, e.g. drowsiness, lethargy, dizziness, ataxia, coma, respiratory depression, hypoventilation and hypotension.

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

Treatment:
The following counter-measures should be taken:

- Removal of tablets ingested - possibly by gastric lavage, performed with caution in comatose patients.
- Intravenous administration of a glucocorticoid eg. hydrocortisone.
- Measures to increase plasma volume.
- Administration of oxygen

- Intravenous administration of vaso-active drugs eg. noradrenaline
- Artificial respiration if required
- Haemoperfusion may be considered.

PRESENTATION

Tablets: containing aminoglutethimide 250 mg (white to yellowish white, round, scored on one side, printed with "GG" on scored side, "CG" on reverse): containers of 100.

SPONSOR

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