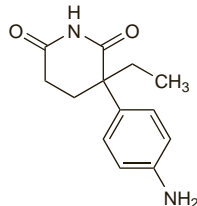


Aminoglutethimide (BAN, rINN) ⊗

Aminoglutethimid; Aminoglutéthimide; Aminoglutethimidum; Aminoglutetimid; Aminoglutetimida; Aminoglutetimidas; Aminoglutetimidi; Aminoglutethimide; Ba-16038. 2-(4-Aminophenyl)-2-ethylglutarimide; 3-(4-Aminophenyl)-3-ethylpiperidine-2,6-dione.

АМИНОГЛУТЕТИМИД
C₁₃H₁₆N₂O₂ = 232.3.
CAS — 125-84-8.
ATC — L02B01.
ATC Vet — QL02BG01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.

Ph. Eur. 6.2 (Aminoglutethimide). A white or slightly yellow, crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol.

USP 31 (Aminoglutethimide). A white or creamy-white, fine, crystalline powder. Very slightly soluble in water; readily soluble in most organic solvents. It forms water-soluble salts with strong acids. The pH of a 0.1% solution in dilute methyl alcohol (1 in 20) is between 6.2 and 7.3.

Adverse Effects

The most frequent adverse effects reported with aminoglutethimide include drowsiness, lethargy, and skin rashes (sometimes with fever); these generally diminish after the first 6 weeks of therapy. Dizziness and nausea occasionally occur. Leucopenia, thrombocytopenia, agranulocytosis, or severe pancytopenia have occurred rarely. Adrenal insufficiency may rarely occur, and there have been reports of other endocrine disturbances including hypothyroidism, and virilisation. Other rare effects include ataxia, headache, depression, gastrointestinal disturbances, hypercholesterolaemia, and orthostatic hypotension.

Overdosage may lead to CNS depression and impairment of consciousness, electrolyte disturbances, and respiratory depression.

Effects on the liver. Aminoglutethimide has been associated with reports of cholestatic jaundice, accompanied by rash^{1,2} and fever,² and probably due to an idiosyncratic hypersensitivity reaction.¹ It has been suggested that liver function tests should be carried out in patients receiving aminoglutethimide who develop fever and eruptions.²

1. Gerber SB, Miller KB. Cholestatic jaundice and aminoglutethimide. *Ann Intern Med* 1982; **97**: 138.
2. Perrault DJ, Domovitch E. Aminoglutethimide and cholestasis. *Ann Intern Med* 1984; **100**: 160.

Effects on the lungs. Pulmonary infiltrates in a patient who developed progressive dyspnoea on starting therapy with aminoglutethimide were found to be due to diffuse alveolar damage and haemorrhage; thrombocytopenia was present but prothrombin and bleeding times were normal. The patient's gas exchange and chest radiographs improved on stopping aminoglutethimide and giving corticosteroids.¹ Blood and pulmonary eosinophilia, which resolved on stopping aminoglutethimide therapy, has also been reported.²

1. Rodman DM, et al. Aminoglutethimide, alveolar damage, and hemorrhage. *Ann Intern Med* 1986; **105**: 633.
2. Bell SC, Anderson EG. Pulmonary eosinophilia associated with aminoglutethimide. *Aust N Z J Med* 1998; **28**: 670-1.

Lupus. SLE occurred in a patient who received aminoglutethimide, and resolved when the drug was withdrawn.¹ In another report, however, a patient with a lupus-like syndrome had a reduction in disease activity when tamoxifen therapy was changed to aminoglutethimide.²

1. McCracken M, et al. Systemic lupus erythematosus induced by aminoglutethimide. *BMJ* 1980; **281**: 1254.
2. Etherington J, et al. Effect of aminoglutethimide on the activity of a case of a connective tissue disorder with features of systemic lupus erythematosus. *Lupus* 1993; **2**: 387.

Precautions

Aminoglutethimide inhibits adrenal steroid production so supplementary glucocorticoid therapy with hydrocortisone must normally be given, although supplementation may not be necessary in patients with Cushing's syndrome. Some patients also require a mineralocorticoid. It has been suggested that aminoglutethimide should be temporarily withdrawn in patients who undergo shock or trauma, or develop intercurrent infection.

Blood pressure, blood counts, and serum electrolytes should be regularly monitored during aminoglutethimide therapy and periodic monitoring of liver and thyroid function is recommended.

Aminoglutethimide should not be given during pregnancy as pseudohermaphroditism may occur in the fetus.

The symbol † denotes a preparation no longer actively marketed

Aminoglutethimide frequently causes drowsiness: patients so affected should not drive or operate machinery.

Porphyria. Aminoglutethimide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The rate of metabolism of some drugs is increased by aminoglutethimide; patients also taking warfarin or other coumarin anticoagulants, theophylline, tamoxifen, medroxyprogesterone, or oral hypoglycaemics, may require increased dosages of these drugs. The metabolism of dexamethasone is also accelerated, which limits its value for corticosteroid supplementation in patients receiving aminoglutethimide. Use with diuretics may lead to hyponatraemia, while alcohol may potentiate the central effects of aminoglutethimide.

♦ See also references to aminoglutethimide's interactions with *digitoxin* (p.1259), *theophylline* (p.1144), *progestogens* (p.2126), *tamoxifen* (see Antineoplastics, p.774), and *anticoagulants* (under Warfarin, p.1429).

Pharmacokinetics

Aminoglutethimide is well absorbed after oral doses, with peak plasma concentrations occurring after 1 to 4 hours. It is metabolised in the liver, primarily to *N*-hydroxylaminoglutethimide and *N*-acetylaminoglutethimide, and appears to induce its own metabolism. The half-life, which is reported to be about 13 hours after a single dose, is decreased to around 9 hours after about 2 weeks of continuous therapy. Aminoglutethimide is excreted in urine, about half a dose being excreted unchanged and the remainder as metabolites. Only about 20 to 25% of a dose is bound to plasma protein.

Half-life. A study in 17 patients showed that the plasma half-life of aminoglutethimide had a mean value of 15.5 hours after single doses but fell to 8.9 hours during multiple-dose therapy.¹ This marked reduction could largely be attributed to a decrease in the volume of distribution; auto-induction of metabolism might be of less importance in decreasing half-life than had been previously suggested.

1. Lønning PE, et al. Single-dose and steady-state pharmacokinetics of aminoglutethimide. *Clin Pharmacokinet* 1985; **10**: 353-64.

Uses and Administration

Aminoglutethimide is an analogue of glutethimide (p.1000) and was formerly used for its weak anticonvulsant properties. Aminoglutethimide blocks the production of adrenal steroids and acts as an aromatase inhibitor to block the conversion of androgens to oestrogens (the major source of oestrogens in women without ovarian function). It was used in the treatment of metastatic breast cancer (p.661) in postmenopausal or oophorectomised women and as palliative treatment in men with advanced prostatic cancer (p.671).

Aminoglutethimide has also been used in the treatment of Cushing's syndrome (p.2344). Usual oral doses range from 1 to 2 g daily, in divided doses.

The *dextro*-isomer of aminoglutethimide, dexaminoglutethimide has been investigated.

Preparations

BP 2008: Aminoglutethimide Tablets;
USP 31: Aminoglutethimide Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Orimeten†; **Austral.:** Cytadren; **Austria:** Orimeten†; **Belg.:** Orimeten†; **Braz.:** Orimeten†; **Chile:** Orimeten†; **Cz.:** Orimeten†; **Fr.:** Orimeten†; **Ger.:** Orimeten†; **Hong Kong:** Orimeten†; **Ital.:** Orimeten†; **Malaysia:** Orimeten†; **Neth.:** Orimeten†; **NZ:** Cytadren†; **Rus.:** Mamomit (Мамомит); **Orimeten** (Ориметен)†; **S.Afr.:** Orimeten†; **Spain:** Orimeten†; **Switz.:** Orimeten†; **UK:** Orimeten†; **USA:** Cytadren†.

5-Aminolevulinic Acid

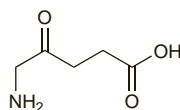
ALA; 5-ALA; δ-Aminolaevalinic Acid; 5-Aminolaevalinic Acid; 5-Aminolevulinico, ácido. 5-Amino-4-oxopentanoic acid.

C₅H₉NO₃ = 131.1.

CAS — 106-60-5.

ATC — L01XD04.

ATC Vet — QL01XD04.

**Aminolevulinic Acid Hydrochloride** (USAN)

Aminolaevalinic Acid Hydrochloride; Aminolevulinico, hidrocioruro ácido. 5-Aminolevulinic acid hydrochloride.

C₅H₉NO₃·HCl = 167.6.

CAS — 5451-09-2.

ATC — L01XD04.

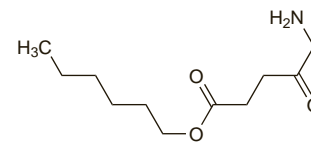
ATC Vet — QL01XD04.

Hexaminolevulinate Hydrochloride (USAN)

P-1026. Hexyl 5-amino-4-oxopentanoate hydrochloride.

C₁₁H₂₁NO₃·HCl = 251.8.

CAS — 140898-91-5.



(hexaminolevulinate)

Methyl Aminolevulinate Hydrochloride (USAN)

Methyl Aminolaevalinate Hydrochloride; Metilaminolevulinato, hidrocioruro de; P-1202. Methyl 5-amino-4-oxopentanoate hydrochloride.

C₆H₁₁NO₃·HCl = 181.6.

CAS — 79416-27-6.

ATC — L01XD03.

ATC Vet — QL01XD03.

Adverse Effects and Precautions

The mechanism of action of topical 5-aminolevulinic acid or its derivatives generally results in local phototoxicity, manifest as a localised burning or stinging sensation, erythema, oedema, pruritus, scabbing, or pain. Symptoms are usually mild to moderate, and transient. During treatment, patients should be advised to avoid sunlight or prolonged exposure to bright light.

Other common adverse effects on the skin include scaling or crusting, ulceration, suppuration, blistering, bleeding, sensation of heat, erosion or exfoliation, and skin infection. Urticaria, rash, and changes in skin pigmentation may also occur. Application site discharge, eczema, and allergic contact dermatitis have been reported. Other common adverse effects include paraesthesia and headache. Nausea, fatigue, eye swelling or eye pain, and wound haemorrhage have been reported.

Handling. US licensed product information warns that nitrile gloves should be worn during application and removal of methyl aminolevulinic acid hydrochloride cream; vinyl or latex gloves do not provide adequate protection.

Hypersensitivity. Allergic reactions to aminolevulinic acid and methyl aminolevulinate² have been reported.

1. Gniazdowska B, et al. Allergic contact dermatitis from δ-aminolevulinic acid used for photodynamic therapy. *Contact Dermatitis* 1998; **38**: 348-9.
2. Wulf HC, Philipsen P. Allergic contact dermatitis to 5-aminolaevalinic acid methyl ester but not to 5-aminolaevalinic acid after photodynamic therapy. *Br J Dermatol* 2004; **150**: 143-5.

Porphyria. 5-Aminolevulinic acid and its derivatives are considered to be unsafe in patients with porphyria.

Interactions

Use with other known photosensitisers such as griseofulvin, thiazide diuretics, sulfonyleureas, phenothiazines, sulfonamides, and tetracyclines might increase the photosensitivity reaction commonly seen with 5-aminolevulinic acid or its derivatives.

St John's wort. A patient taking St John's wort had a pronounced phototoxic reaction consisting of an erythematous rash and swelling of the face, neck, and hands, 6 hours after receiving oral aminolevulinic acid. Although both drugs have been associated with photosensitivity, the authors suggested a synergistic effect had occurred. Tests *in vitro* appeared to confirm this.¹

1. Ladner DP, et al. Synergistic toxicity of δ-aminolaevalinic acid-induced protoporphyrin IX used for photodiagnosis and hypericum extract, a herbal antidepressant. *Br J Dermatol* 2001; **144**: 916-8.

Pharmacokinetics

After intravenous and oral doses of aminolevulinic acid hydrochloride equivalent to 100 mg of aminolevulinic acid, the mean half-life of aminolevulinic acid is stated to be about 0.83 hours and 0.7 hours, respectively; oral bioavailability is about 50 to 60%. *In-vitro* studies of dermal absorption found that the mean cumulative absorption of methyl aminolevulinate

The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p.vii)