

Clorazepate

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Introduction

Clorazepate is a **benzodiazepine** compound which is rapidly decarboxylated in the stomach to the active metabolite, N-desmethyldiazepam. It is thus classified as a prodrug and the metabolite has all the properties of the benzodiazepine group of drugs. It has anxiolytic, sedative, anticonvulsant and muscle relaxant properties.

Nomenclature

Name of the Clinical Form Clorazepate dipotassium

Related Names chlorazepatic acid; clorazepic acid; ClorazeCaps, GenENE, Tranxene; Abbott-35616; AH-3232; Dikalii Clorazepas; 7 chloro 2,3 dihydro 2 oxo 5 phenyl 1h 1,4 benzodiazepine 3 carboxylic acid; 7 chloro 5 phenyl 2,2 dihydroxy 2,3 dihydro 1 h benzo[f] 1,4 diazepine 3 carboxylic acid; chlorazepate; chloroazepate

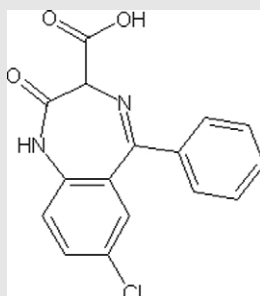
Source: [EMTREE](#)

Chemical Names Dipotassium-7-chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1H-1,4-benzodiazepine-3-carboxylicacid; Potassium 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-carboxylatewith KOH; 7 chloro 2,3 dihydro 2 oxo 5 phenyl 1h 1,4 benzodiazepine 3carboxylic acid; 7 chloro 5 phenyl 2,2 dihydroxy 2,3 dihydro 1 h benzo[f] 1,4diazepine 3 carboxylic acid

CAS Number 57109-90-7

Basic Chemistry

Chemical Structure
Structure



Chemical Formula C₁₆ H₁₁ Cl N₂ O₃

Properties

Physical Properties	White or light yellow crystals.
Molecular Weight	314.727
Solubility	The dipotassium salt is freely soluble in water and poorly soluble in ethanol.

Human Pharmacokinetics

Clorazepate is rapidly decarboxylated in the gastrointestinal system to the biologically active compound, N-desmethyldiazepam, which is absorbed entirely. The metabolite reaches peak concentration in less than an hour. As N-desmethyldiazepam has a long half-life (>72 hours), clorazepate may be administered once a day.

Pharmacokinetic Properties

	Value	Units	Prep. and Route of Admin.	Reference	Comments
Absorption					
Bioavailability	91	%	p.o.	Hardman and Limbird (2001)	Clorazepate is a prodrug for nordiazepam and these pharmacokinetic values were derived for nordazepam after oral administration of clorazepate.
Distribution					
Volume of Distribution	1.24	l/kg	i.v.	Hardman and Limbird (2001)	
Plasma Protein Binding	97.5	%	p.o.	Hardman and Limbird (2001)	
Metabolism					
Plasma Half-Life	93	hrs	i.v.	Hardman and Limbird (2001)	
Bio Half-Life					
Clearance	0.17	ml/min/kg	i.v.	Hardman and Limbird (2001)	
Routes of Elimination	Urine				

Targets-Pharmacodynamics

In common with all **benzodiazepine drugs**, clorazepate (nordiazepam) interacts with the **GABA-A receptor** complex in the **central nervous system** to facilitate inhibitory GABAergic neurotransmission. This action is through positive allosteric modulation at the complex, resulting in an increased influx of chloride ions.

Target Name(s):

GABA-A receptor

Therapeutics

Benzodiazepines are indicated for the short-term relief of severe anxiety, but long-term use should be avoided [British National Formulary \(2003\)](#). The main use of clorazepate is for the treatment of anxiety. It may also be used for **insomnia**, epilepsy, pre-anesthetic medication, and **alcohol** withdrawal.

Indications

	Value	Units	Prep. and Route of Admin.	Reference	Comments
Anxiety					
Dosage	7.5–22.5	mg	Clorazepate dipotassium p.o.	British National Formulary (2003)	May be administered in 2–3 divided doses or as 15 mg at bedtime.

Contraindications

Contraindications to clorazepate include known hypersensitivity to **benzodiazepines** and acute pulmonary insufficiency.

Adverse Effects

Adverse effects of clorazepate include confusion and ataxia (especially in the elderly), sedation, amnesia, muscle weakness and dependence following long-term use.

Agent-Agent Interactions

Agent Name	Mode of Interaction
Alcohol	Synergistic effect with clorazepate (increased sedation).
Barbiturates	Synergistic effect with clorazepate (increased sedation).
Opioid analgesics	Synergistic effect with clorazepate (increased sedation).
Neuroleptics	Synergistic effect with clorazepate (increased sedation).

Pre-Clinical Research

In a paradigm to test anxiety in animals, clorazepate was shown to increase the time spent in the light compartment of a light/dark choice situation in mice [Belzung et al \(1987\)](#). Clorazepate has also been shown to delay both amygdaloid- and hippocampal-kindled seizures in rats [Amano et al \(1999\)](#) and inhibit pentylenetetrazol-induced convulsions in mice [Frey and Scherkl \(1988\)](#). GABA-induced currents in *Xenopus* oocytes injected with chick brain mRNA were enhanced in the presence of clorazepate [Sigel and Baur \(1988\)](#).

Pharmacokinetics

Potency

Value	Units	Organ/ Tissue	Prep. and Route of Admin.	Cell Line/ Type	Effects	Exp. End Point	Reference	Comments
Mouse								
DOSE 1–4	mg/kg				Anxiolytic		Belzung et al (1987)	Light/dark choice situation.
LD50 700	mg/kg		p.o.				The Merck Index (2001)	
LD50 290	mg/kg		i.p.				The Merck Index (2001)	
ED50 12	mg/kg		i.v.		Anticonvulsant		Frey and Scherkl (1988)	Pentylenetetrazol-induced convulsions
Rat								
DOSE 1	mg/kg		Dipotassium Clorazepate i.p.		Delayed hippocampal-kindled seizures.		Amano et al (1999)	
DOSE 5	mg/kg		Dipotassium Clorazepate i.p.		Delayed amygdaloid-kindled seizures		Amano et al (1999)	
LD50 >1000	mg/kg		p.o.				The Merck Index (2001)	

Other Information – Web Sites

A PubChem Compound summary is available at: <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=2809>

Journal Citations

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Further Reading

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