Cetiedil Citrate *(USAN, rINNM)*

Cétiédil, Citrate de; Cetiedili Citras; Citrato de cetiedil. 2-(Perhydroazepin-1-yl)ethyl α-cyclohexyl-α-(3-thienyl)acetate dihydrogen citrate monohydrate.

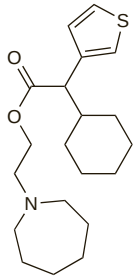
Цетиедила Цитрат

$C_{20}H_{31}NO_2S,C_6H_8O_7,H_2O$ = 559.7.

CAS — 14176-10-4 (cetiedil); 16286-69-4 (anhydrous cetiedil citrate).

ATC — C04AX26.

ATC Vet — QC04AX26.



(cetiedil)

Profile

Cetiedil citrate is a vasodilator with antimuscarinic activity that has been used in the management of peripheral vascular disease.

Chlorothiazide *(BAN, rINN)* ⊗

Chlorothiazid; Chlorothiazidum; Chlorotiazidas; Chlorotiazyd; Clorotiazida; Klooritiatsidi; Klorotiazid; Klortiazid. 6-Chloro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

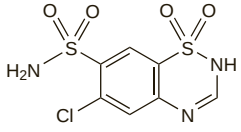
Хлоротиазид

$C_7H_6ClN_3O_4S_2$ = 295.7.

CAS — 58-94-6.

ATC — C03AA04.

ATC Vet — QC03AA04.



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

Ph. Eur. 6.2 (Chlorothiazide). A white or almost white crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; sparingly soluble in acetone. It dissolves in dilute solutions of alkali hydroxides.

USP 31 (Chlorothiazide). A white or practically white, odourless, crystalline powder. Very slightly soluble in water; practically insoluble in chloroform, in ether, and in benzene; freely soluble in dimethylformamide and dimethyl sulfoxide; slightly soluble in methyl alcohol and in pyridine. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Alkaline solutions undergo decomposition due to hydrolysis upon standing or heating.

Chlorothiazide Sodium *(BANM, USAN, rINNM)* ⊗

Chlorothiazide Sodique; Clorotiazida sódica; Natrii Chlorothiazidum; Sodium Chlorothiazide.

Натрий Хлоротиазид

$C_7H_5ClN_3NaO_4S_2$ = 317.7.

CAS — 7085-44-1.

ATC — C03AA04.

ATC Vet — QC03AA04.

Pharmacopoeias. *US* includes Chlorothiazide Sodium for Injection.

Incompatibility. The alkaline nature of chlorothiazide in injectable form suggests that incompatibilities with acidic drugs could be expected; US licensed product information states that the injection may be diluted with glucose or sodium chloride solutions.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307. Chlorothiazide sodium injection is alkaline: when giving chlorothiazide by intravenous infusion, care should be taken to ensure that extravasation does not occur.

Breast feeding. Chlorothiazide is distributed into breast milk in small amounts. A single 500-mg oral dose of chlorothiazide was given[1] to 11 lactating women and blood and milk samples taken after 1, 2, and 3 hours; all the samples had concentrations below 1 microgram/mL and it was calculated that an infant would receive no more than 1 mg of drug each day. The American Academy of Pediatrics states that no adverse effects have been seen in infants and therefore considers[2] that chlorothiazide is usually compatible with breast feeding.

1. Werthmann MW, Krees SV. Excretion of chlorothiazide in human breast milk. *J Pediatr* 1972; **81:** 781–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Chlorothiazide is incompletely and variably absorbed from the gastrointestinal tract. It has been estimated to have a plasma half-life of 45 to 120 minutes although the clinical effects may last for up to about 12 hours. It is excreted unchanged in the urine. Chlorothiazide crosses the placental barrier and small amounts are reported to be distributed into breast milk.

Uses and Administration

Chlorothiazide is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide (p.1310). It is used for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

After oral doses of chlorothiazide diuresis usually occurs in about 2 hours, reaches a maximum at about 4 hours, and is maintained for 6 to 12 hours.

In the treatment of **oedema** the usual dose of chlorothiazide is 0.25 to 1 g orally once or twice daily; therapy on alternate days or on 3 to 5 days weekly may be adequate. The dose should not normally exceed 2 g daily.

In the treatment of **hypertension** the usual initial dose is 250 to 500 mg daily orally, given as a single or divided dose. A dose of 125 mg may be adequate in some patients. Patients may rarely require up to 1 g daily.

For the use of chlorothiazide in children, see below.

Chlorothiazide has also been given intravenously as the sodium salt, in doses similar to those given orally. Chlorothiazide sodium 537 mg is equivalent to about 500 mg of chlorothiazide. It is not suitable for subcutaneous or intramuscular injection and extravasation should be avoided. The diuretic effect lasts for up to 2 hours after intravenous injection.

Administration in children. Chlorothiazide may be used in children for the management of *heart failure* or *hypertension*. Usual oral doses are as follows:

- neonates and infants aged 1 to 6 months: 10 to 20 mg/kg twice daily
- age 6 months to 12 years: 10 mg/kg twice daily, to a maximum of 1 g daily
- age 12 to 18 years: 0.25 to 1 g once daily or 125 to 500 mg twice daily

For *diabetes insipidus* in children, the *BNFC* suggests an oral dose of 10 to 20 mg/kg twice daily, to a maximum of 1 g daily.

Chlorothiazide also has a hyperglycaemic effect and has been used in children with *chronic hypoglycaemia* (see under Uses of Glucagon, p.1447). It is usually given with diazoxide and has the added benefit of reducing diazoxide-associated sodium and water retention. The *BNFC* suggests an oral dose of 3 to 5 mg/kg twice daily.

Preparations

USP 31: Chlorothiazide Oral Suspension; Chlorothiazide Sodium for Injection; Chlorothiazide Tablets; Methyldopa and Chlorothiazide Tablets; Reserpine and Chlorothiazide Tablets.

Proprietary Preparations (details are given in Part 3)

Singapore: Chlorzide†; ***USA:*** Diurigen; Diuril.

Multi-ingredient: ***Canad.:*** Supres†; ***Gr.:*** Neourizine; ***USA:*** Aldoclor; Diupres.

Chlortalidone *(BAN, rINN)* ⊗

Chlorotalidon; Chlortalidon; Chlortalidonas; Chlortalidonum; Chlorthalidone *(USAN)*; Clorotalidona; Clortalidona; G-33182; Klooritaldoni; Klórtalidon; Klortalidon; NSC-69200. 2-Chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl)benzenesulphonamide

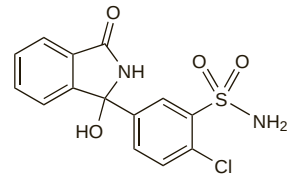
Хлорталидон

$C_{14}H_{11}ClN_2O_4S$ = 338.8.

CAS — 77-36-1.

ATC — C03BA04.

ATC Vet — QC03BA04.



NOTE. Compounded preparations of chlortalidone may be represented by the following names:

- Co-tenidone (*BAN*)—chlortalidone 1 part and atenolol 4 parts (w/w).

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

Ph. Eur. 6.2 (Chlortalidone). A white or yellowish-white powder. Very slightly soluble in water; soluble in acetone and in methyl alcohol; practically insoluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. It exhibits polymorphism.

USP 31 (Chlorthalidone). A white or yellowish-white crystalline powder. Practically insoluble in water, in chloroform, and in ether; slightly soluble in alcohol; soluble in methyl alcohol.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Breast feeding. Chlortalidone is distributed into breast milk, but a study[1] in 9 women given a dose of 50 mg daily found that the concentration in milk was only about 5% of that in the blood. However, caution was advised since chlortalidone elimination may be slower in neonates. The American Academy of Pediatrics considers[2] that chlortalidone is usually compatible with breast feeding.

1. Mulley BA, *et al.* Placental transfer of chlorthalidone and its elimination in maternal milk. *Eur J Clin Pharmacol* 1978; **13:** 129–31.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

As for Hydrochlorothiazide, p.1309.

Anticoagulants. For references to the interaction between *warfarin* and chlortalidone, see p.1430.

Pharmacokinetics

Chlortalidone is erratically absorbed from the gastrointestinal tract and bioavailability varies according to the preparation used. It has a prolonged elimination half-life from plasma and blood of 40 to 60 hours and is highly bound to red blood cells; the receptor to which it is bound has been identified as carbonic anhydrase. Chlortalidone is much less strongly bound to plasma proteins. Chlortalidone is mainly excreted unchanged in the urine. It crosses the placental barrier and is distributed into breast milk.

◊ References.

1. Riess W, *et al.* Pharmacokinetic studies with chlorthalidone (Hygroton) in man. *Eur J Clin Pharmacol* 1977; **12:** 375–82.
2. Fleuren HLJ, *et al.* Absolute bioavailability of chlorthalidone in man: a cross-over study after intravenous and oral administration. *Eur J Clin Pharmacol* 1979; **15:** 35–50.
3. Fleuren HLJ, *et al.* Dose-dependent urinary excretion of chlorthalidone. *Clin Pharmacol Ther* 1979; **25:** 806–12.
4. Mulley BA, *et al.* Pharmacokinetics of chlorthalidone: dependence of biological half life on blood carbonic anhydrase levels. *Eur J Clin Pharmacol* 1980; **17:** 203–7.

Uses and Administration

Chlortalidone is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1310) even though it does not contain a thiazide ring system. It is given orally for hypertension