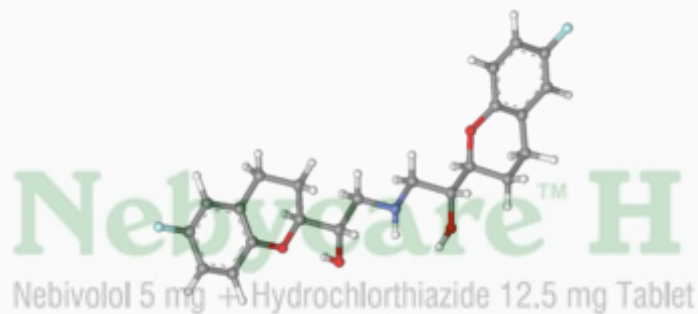
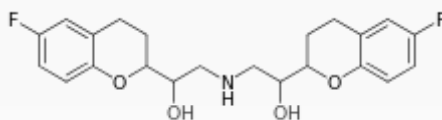


# Nebivolol

Nebivolol



## Systematic (IUPAC) name

1-(6-Fluorochroman-2-yl)-{[2-(6-fluorochroman-2-yl)-2-hydroxy-ethyl]amino}ethanol

OR

2,2'-Azanediylbis(1-(6-fluorochroman-2-yl)ethanol)

OR

1-(6-Fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-{{[2-(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-hydroxyethyl]amino}ethan-1-ol

## Clinical data

### Trade names

Nebilet, Bystolic

### AHFS/Drugs.com

[monograph](#)

### MedlinePlus

[a608029](#)

### Licence data

[US FDA:link](#)

### Pregnancy cat.

C (US)

### Legal status

[POM \(UK\)](#) [R-only \(US\)](#)

<b><u>Routes</u></b>	Oral
<b>Pharmacokinetic data</b>	
<b><u>Protein binding</u></b>	98%
<b><u>Metabolism</u></b>	<u>Hepatic</u> (CYP2D6-mediated)
<b><u>Half-life</u></b>	10 hours
<b><u>Excretion</u></b>	<u>Renal</u> and fecal
 <b>Identifiers</b> Nebivolol 5 mg + Hydrochlorothiazide 12.5 mg Tablet	
<b><u>CAS number</u></b>	<u>99200-09-6</u>
<b><u>ATC code</u></b>	<u>C07AB12</u>
<b><u>PubChem</u></b>	<u>CID 71301</u>
<b><u>DrugBank</u></b>	<u>DB04861</u>
<b><u>ChemSpider</u></b>	<u>64421</u>
<b><u>UNII</u></b>	<u>030Y90569U</u>
<b><u>KEGG</u></b>	<u>D05127</u>
<b><u>ChEMBL</u></b>	<u>CHEMBL434394</u>
<b>Chemical data</b>	
<b><u>Formula</u></b>	<u>C<sub>22</sub>H<sub>25</sub>F<sub>2</sub>NO<sub>4</sub></u>
<b><u>Mol. mass</u></b>	405.435 <u>g/mol</u>
<b><u>SMILES</u></b>	<ul style="list-style-type: none"> <li><chem>Fc4cc1c(OC(CC1)C(O)CNCC(O)C3Oc2ccc(F)cc2CC3)cc4</chem></li> </ul>

### InChI

InChI=1S/C22H25F2NO4/c23-15-3-7-19-13(9-15)1-5-21(28-19)17(26)11-25-12-18(27)22-6-2-14-10-16(24)4-8-20(14)29-22/h3-4,7-10,17-18,21-22,25-27H,1-2,5-6,11-12H2

Key:KOHIRBRYDXPAMZ-UHFFFAOYSA-N

**Nebivolol** is a  $\beta_1$  receptor blocker with nitric oxide-potentiating vasodilatory effect used in treatment of hypertension and, in Europe, also for left ventricular failure.<sup>[1]</sup> It is highly cardioselective under certain circumstances.<sup>[1]</sup>

## Pharmacology and biochemistry

### **$\beta_1$ Selectivity**

Beta blockers help patients with cardiovascular disease by blocking  $\beta$  receptors, while many of the side-effects of these medications are caused by their blockade of  $\beta_2$  receptors.<sup>[2]</sup> For this reason, beta blockers that selectively block  $\beta_1$  receptors (termed cardioselective or  $\beta_1$ -selective beta blockers) produce fewer adverse effects (for instance, bronchoconstriction) than those drugs that non-selectively block both  $\beta_1$  and  $\beta_2$  receptors. Nebivolol has been marketed by Cipla Ltd under brand name Nebicip; by Forest Laboratories under the name Bystolic; by Micro Labs under the brand name Nebilong; ; and by Menarini under the names Hypoloc, Lobivon, Nebilet, Nebilox, Nobiten, and Temerit. In a laboratory experiment conducted on biopsied heart tissue, nebivolol proved to be the most  $\beta_1$ -selective of the  $\beta$ -blockers tested, being approximately 3.5 times more  $\beta_1$ -selective than bisoprolol.<sup>[3]</sup> However, the drug's receptor selectivity in humans is more complex and depends on the drug dose and the genetic profile of the patient taking the medication.<sup>[4]</sup> The drug is highly cardioselective at 5 mg.<sup>[5]</sup> However, at doses above 10 mg, nebivolol loses its cardioselectivity and blocks both  $\beta_1$  and  $\beta_2$  receptors.<sup>[4]</sup> (While the recommended starting dose of nebivolol is 5 mg, sufficient control of blood pressure may require doses up to 40 mg).<sup>[4]</sup> Furthermore, nebivolol is also not cardioselective when taken by patients with a genetic makeup that makes them "poor metabolizers" of nebivolol (and other drugs) or with CYP2D6 inhibitors.<sup>[4]</sup> As many as 1 in 10 whites and even more blacks are poor CYP2D6 metabolizers and therefore might benefit less from nebivolol's cardioselectivity although currently there are no directly comparable studies.

### **Vasodilator action**

Nebivolol is unique as a beta-blocker.<sup>[6]</sup> Unlike carvedilol, it has a nitric oxide (NO)-potentiating, vasodilatory effect.<sup>[7][8]</sup> Along with labetalol, celiprolol and carvedilol, it is one of four beta blockers to cause dilation of blood vessels in addition to effects on the heart.<sup>[8]</sup> However, recent studies question the clinical relevance of this property to Nebivolol's efficacy.<sup>[9]</sup>

### **Antihypertensive effect**

Nebivolol lowers blood pressure (BP) by reducing peripheral vascular resistance, and significantly increases stroke volume with preservation of cardiac output.<sup>[10]</sup> The net hemodynamic effect of nebivolol is the result of a balance between the depressant effects of beta-blockade and an action that maintains cardiac output.<sup>[11]</sup> Antihypertensive responses were significantly higher with nebivolol than with placebo in trials enrolling patient groups considered representative of the U.S. hypertensive population, in Black patients, and in those receiving concurrent treatment with other antihypertensive drugs.<sup>[12]</sup>

### **Pharmacology of side-effect**

Several studies have suggested that nebivolol has reduced typical beta-blocker-related side effects, such as fatigue, clinical depression, bradycardia, or impotence.<sup>[13][14][15]</sup> However, according to the FDA<sup>[16]</sup>

“ Bystolic is associated with a number of serious risks. Bystolic is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe [hepatic](#) impairment (Child-Pugh > B) and in patients who are hypersensitive to any component of the product. Bystolic therapy is also associated with warnings regarding abrupt cessation of therapy, cardiac failure, angina and acute myocardial infarction, bronchospastic diseases, anesthesia and major surgery, diabetes and hypoglycemia, thyrotoxicosis, peripheral vascular disease, non-dihydropyridine calcium channel blockers use, as well as precautions regarding use with CYP2D6 inhibitors, impaired renal and hepatic function, and anaphylactic reactions. Finally, Bystolic is associated with other risks as described in the Adverse Reactions section of its PI. For example, a number of treatment-emergent adverse events with an incidence greater than or equal to 1 percent in Bystolic-treated patients and at a higher frequency than placebo-treated patients were identified in clinical studies, including headache, fatigue, and dizziness. ”

## FDA warning letter about advertising claims

In late August 2008, the FDA issued a [Warning Letter](#) to Forest Laboratories citing exaggerated and misleading claims in their launch journal ad, in particular over claims of superiority and novelty of action.<sup>[16]</sup>

## Contraindications

- Hepatic insufficiency
- Children
- Pregnancy
- Lactation

## Adverse drug reactions

- Headache
- [Paresthesia](#)
- Dizziness

**Nebycare™ H**  
Nebivolol 5 mg + Hydrochlorothiazide 12.5 mg Tablet

## History

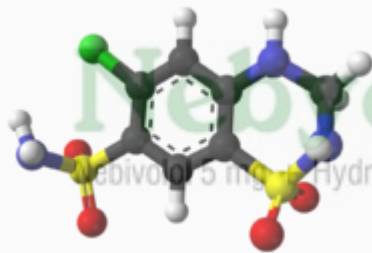
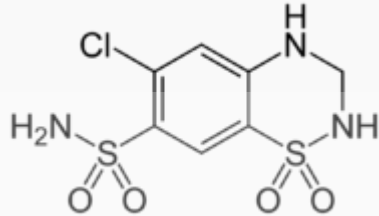
Mylan Laboratories licensed the U.S. and Canadian rights to nebivolol from [Janssen Pharmaceutica](#) N.V. in 2001. Nebivolol is already registered and successfully marketed in more than 50 countries, including the United States where it is marketed under the brand name Bystolic from [Mylan Laboratories](#) and [Forest Laboratories](#). Nebivolol is manufactured by Forest Laboratories.

## References

1. <sup>▲▲</sup> de Boer RA, Voors AA, van Veldhuisen DJ (July 2007). "Nebivolol: third-generation beta-blockade". *Expert Opin Pharmacother* **8** (10): 1539–50. doi:10.1517/14656566.8.10.1539. PMID 17661735.
2. <sup>▲</sup> Tafreshi MJ, Weinacker AB (August 1999). "Beta-adrenergic-blocking agents in bronchospastic diseases: a therapeutic dilemma". *Pharmacotherapy* **19** (8): 974–8. doi:10.1592/phco.19.11.974.31575. PMID 10453968.
3. <sup>▲</sup> Bundkirchen A, Brixius K, Böck B, Nguyen Q, Schwinger RH (January 2003). "Beta 1-adrenoceptor selectivity of nebivolol and bisoprolol. A comparison of [3H]CGP 12.177 and [125I]iodocyanopindolol binding studies". *Eur. J. Pharmacol.* **460** (1): 19–26. doi:10.1016/S0014-2999(02)02875-3. PMID 12535855.
4. <sup>▲▲▲▲</sup> "Prescribing information for Bystolic". Retrieved 2009-06-11.
5. <sup>▲</sup> Nuttall SL, Routledge HC, Kendall MJ (June 2003). "A comparison of the beta1-selectivity of three beta1-selective beta-blockers". *J Clin Pharm Ther* **28** (3): 179–86. doi:10.1046/j.1365-2710.2003.00477.x. PMID 12795776.
6. <sup>▲</sup> Agabiti Rossi E, Rizzoni D (2007). "Metabolic profile of nebivolol, a beta-adrenoceptor antagonist with unique characteristics". *Drugs* **67** (8): 1097–107. doi:10.2165/00003495-200767080-00001. PMID 17521213.
7. <sup>▲</sup> Weiss R (2006). "Nebivolol: a novel beta-blocker with nitric oxide-induced vasodilatation". *Vasc Health Risk Manag* **2** (3): 303–8. doi:10.2147/vhrm.2006.2.3.303. PMC 1993984. PMID 17326335.
8. <sup>▲▲</sup> Bakris G (May 2009). "An in-depth analysis of vasodilation in the management of hypertension: focus on adrenergic blockade". *J. Cardiovasc. Pharmacol.* **53** (5): 379–87. doi:10.1097/FJC.0b013e31819fd501. PMID 19454898.
9. <sup>▲</sup> National Prescribing Service (1 March 2010). "Nebivolol (Nebilet) for chronic heart failure". Retrieved 12 March 2010.
10. <sup>▲</sup> Kamp O, Sieswerda GT, Visser CA (August 2003). "Comparison of effects on systolic and diastolic left ventricular function of nebivolol versus atenolol in patients with uncomplicated essential hypertension". *Am. J. Cardiol.* **92** (3): 344–8. doi:10.1016/S0002-9149(03)00645-3. PMID 12881152.
11. <sup>▲</sup> Gielen W, Cleophas TJ, Agrawal R (August 2006). "Nebivolol: a review of its clinical and pharmacological characteristics". *Int J Clin Pharmacol Ther* **44** (8): 344–57. PMID 16961165.
12. <sup>▲</sup> Baldwin CM, Keam SJ. Nebivolol: In the Treatment of Hypertension in the US. *Am J Cardiovasc Drugs* 2009; 9 (4): 253-260. [Link text](#)
13. <sup>▲</sup> Pessina AC (December 2001). "Metabolic effects and safety profile of nebivolol". *J. Cardiovasc. Pharmacol.* **38**, Suppl 3: S33–5. PMID 11811391.
14. <sup>▲</sup> Weber MA (December 2005). "The role of the new beta-blockers in treating cardiovascular disease". *Am. J. Hypertens.* **18** (12 Pt 2): 169S–176S. doi:10.1016/j.amjhyper.2005.09.009. PMID 16373195.
15. <sup>▲</sup> Poirier L, Cl  roux J, Nadeau A, Lacourci  re Y (August 2001). "Effects of nebivolol and atenolol on insulin sensitivity and haemodynamics in hypertensive patients". *J. Hypertens.* **19** (8): 1429–35. doi:10.1097/00004872-200108000-00011. PMID 11518851

# Hydrochlorothiazide

Hydrochlorothiazide



Systematic (IUPAC) name

5-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide

Clinical data

**Trade names** Apo-hydro, Aquazide h, Dichlotride among others, Oretic

**AHFS/Drugs.com** [monograph](#)

**MedlinePlus** [a682571](#)

**Pregnancy category** B (D if used to treat pregnancy-induced hypertension)

**Legal status** R (Prescription only)

**Routes of administration** Oral (capsules, tablets, oral solution)

Pharmacokinetic data

**Bioavailability** Variably absorbed from GI tract. Bioavailability ~ 70%

<b>Metabolism</b>	does not undergo significant metabolism (>95% excreted unchanged in urine) <sup>[1]</sup>
<b>Biological half-life</b>	5.6–14.8 h
<b>Excretion</b>	Primarily excreted unchanged in urine
Identifiers	
<b>CAS Registry Number</b>	<a href="#">58-93-5</a> ✓
<b>ATC code</b>	<a href="#">C03AA03</a>
<b>PubChem</b>	CID: <a href="#">3639</a>
<b>IUPHAR/BPS</b>	<a href="#">4836</a>
<b>DrugBank</b>	<a href="#">DB00999</a> ✓
<b>UNII</b>	<a href="#">0J48LPH2TH</a> ✓
<b>KEGG</b>	<a href="#">D00340</a> ✓
<b>ChEBI</b>	<a href="#">CHEBI:5778</a> ✗
<b>ChEMBL</b>	<a href="#">CHEMBL435</a> ✓
Chemical data	
<b>Formula</b>	<a href="#">C<sub>7</sub>H<sub>7</sub>ClN<sub>2</sub>O<sub>2</sub>S<sub>2</sub></a>
<b>Molecular mass</b>	297.74 g/mol
<b>SMILES</b> <a href="#">[show]</a>	
<b>InChI</b> <a href="#">[show]</a>	
✗ <a href="#">[what is this?]</a> <a href="#">(verify)</a>	

**Hydrochlorothiazide** (abbreviated **HCTZ**, **HCT**, or **HZT**), is a [diuretic](#) medication often used to treat [high blood pressure](#) and [swelling due to fluid build up](#).<sup>[2]</sup> Other uses include [diabetes insipidus](#), [renal tubular acidosis](#), and to decrease the risk of [kidney stones](#) in those with [high calcium level in the urine](#).<sup>[2]</sup> For high blood pressure it is often recommended as a first line

treatment.<sup>[a]</sup><sup>[b]</sup>HCTZ is taken by mouth and may be combined with other [blood pressure medications](#) as a single pill to increase the effectiveness.<sup>[a]</sup>

Potential side effects include poor kidney function, [electrolyte imbalances](#) especially [low blood potassium](#) and less commonly [low blood sodium](#), [gout](#), [high blood sugar](#), and [feeling faint initially upon standing up](#).<sup>[a]</sup> While [allergies](#) to HCTZ are reported to occur more often in those with allergies to [sulfa drugs](#) this association is not well supported.<sup>[a]</sup> It may be used during pregnancy but is not a first line medication in this group.<sup>[a]</sup>

It is in the [thiazide](#) medication class and acts by decreasing the [kidneys'](#) ability to retain water.<sup>[a]</sup> This initially reduces [blood](#) volume, decreasing blood return to the heart and thus [cardiac output](#).<sup>[a]</sup> Long term, however, it is believed to lower [peripheral vascular resistance](#).<sup>[a]</sup>

Two companies, [Merck](#) and [Ciba](#), state they discovered the medication which became commercially available in 1959.<sup>[a]</sup> It is on the [World Health Organization's List of Essential Medicines](#), the most important medications needed in a basic [health system](#).<sup>[a]</sup> In 2008 it was the second most commonly used blood pressure medication in the United States.<sup>[a]</sup> It is available as a [generic drug](#)<sup>[a]</sup> and is relatively affordable.<sup>[a]</sup>

#### Contents

[\[hide\]](#)

- [1Medical uses](#)
- [2Adverse effects](#)
- [3Mechanism of action](#)
- [4Society and culture](#)
  - [4.1Brand names](#)
  - [4.2Sport](#)
- [5See also](#)
- [6References](#)
- [7External links](#)

## Medical uses[\[edit\]](#)

Hydrochlorothiazide is frequently used for the treatment of [hypertension](#), [congestive heart failure](#), symptomatic [edema](#), [diabetes insipidus](#), [renal tubular acidosis](#).<sup>[a]</sup> It is also used for the prevention of [kidney stones](#) in those who have high levels of calcium in their urine.<sup>[a]</sup>

Most of the research supporting the use of thiazide diuretics in hypertension was done using [chlorthalidone](#), a different medication in the same class. Some more recent studies have suggested that chlorthalidone might be the more effective thiazide diuretic.<sup>[a]</sup>

It is also sometimes used for treatment of [hypoparathyroidism](#),<sup>[a]</sup> [hypercalciuria](#), [Dent's disease](#), and [Ménière's disease](#). For diabetes insipidus, the effect of thiazide diuretics is presumably mediated by a hypovolemia-induced increase in proximal sodium and water reabsorption, thereby diminishing water delivery to the ADH-sensitive sites in the collecting tubules and increasing the urine osmolality.

Thiazides are also used in the treatment of [osteoporosis](#). Thiazides decrease mineral bone loss by promoting calcium retention in the kidney, and by directly stimulating [osteoblast](#) differentiation and bone mineral formation.<sup>[a]</sup>

It may be given together with other antihypertensive agents in fixed combination preparations, such as in [hydrochlorothiazide/losartan](#).

## Adverse effects[\[edit\]](#)

- [Hypokalemia](#), or low blood levels of potassium are an occasional side effect. It can be usually prevented by [potassium](#) supplements or by combining hydrochlorothiazide with a [potassium-sparing diuretic](#).

- Other disturbances in the levels of serum electrolytes including [hypomagnesemia](#) (low magnesium), [hyponatremia](#) (low sodium), and [hypercalcemia](#) (high calcium).
- [Hyperuricemia](#), high levels of uric acid in the blood.
- [Hyperglycemia](#), high blood sugar.
- [Hyperlipidemia](#), high cholesterol and triglycerides.
- [Headache](#)
- [Nausea/vomiting](#)
- [Photosensitivity](#)
- [Weight gain](#)
- [Gout](#)
- [Pancreatitis](#)

These side effects increase with the dose of the medication and are most common at doses of greater than 25 mg per day.

Package inserts, based on case reports and observational studies, have reported that an allergy to a [sulfa drug](#) predisposes the patient to cross sensitivity to a thiazide diuretic. A 2005 review of the literature did not find support for this cross-sensitivity.<sup>[u]</sup>

## Mechanism of action<sup>[edit]</sup>

Hydrochlorothiazide belongs to [thiazide](#) class of [diuretics](#). It reduces blood volume by acting on the [kidneys](#) to reduce [sodium](#) (Na<sup>+</sup>) reabsorption in the [distal convoluted tubule](#). The major site of action in the nephron appears on an electroneutral NaCl co-transporter by competing for the chloride site on the transporter. By impairing Na transport in the distal convoluted tubule, hydrochlorothiazide induces a [natriuresis](#) and concomitant water loss. Thiazides increase the reabsorption of calcium in this segment in a manner unrelated to sodium transport.<sup>[u]</sup> Additionally, by other mechanisms, HCTZ is believed to lower [peripheral vascular resistance](#).<sup>[u]</sup>

## Society and culture<sup>[edit]</sup>

Co-Diovan ([valsartan](#) and hydrochlorothiazide)



Benazepril hydrochloride 20 mg / hydrochlorothiazide 25 mg oral tablet

## Brand names<sup>[edit]</sup>

Hydrochlorothiazide is sold both as a [generic drug](#) and under a large number of brand names, including BP Zide 12.5 & 25 (Stadmed), Apo-Hydro, Aquazide H, Dichlotride, Hydrodiuril, HydroSaluric, Hydrochlorot, Microzide, Esidrex, and Oretic.

Hydrochlorothiazide is also used in combination with many other classes of hypertensive drugs such as [ACE inhibitors](#), [angiotensin receptor blockers](#), and [beta blockers](#). These are sold under brand names including Diovan HCT, [Zestoretic](#), Ziacc, Benicar HCT, Olmy-H, Atacand HCT, and Lotensin HCT, Temax-H and others.

## Sport<sup>[edit]</sup>



Hydrochlorothiazide was detected in the [urine](#) of the Russian [cyclist Alexandr Kolobnev](#) during the [2011 Tour de France](#).<sup>[[csc](#)]</sup> Kolobnev was the only cyclist to leave the 2011 race in connection with adverse findings at a doping control.<sup>[[csc](#)]</sup> While hydrochlorothiazide is not itself a performance-enhancing drug, it may be used to mask the use of performance-enhancing drugs, and is classed by the [World Anti-Doping Agency](#) as a "specified substance". Kolobnev was subsequently cleared of all charges of intentional doping.<sup>[[csc](#)]</sup>

See also [\[edit\]](#)

---

- [Benicar HCT](#)
- [Diovan HCT](#)

References [\[edit\]](#)

---

1. **Jump up**<sup>Δ</sup> Beermann B, Groschinsky-Grind M, Rosén A. (1976). "Absorption, metabolism, and excretion of hydrochlorothiazide". *Clin Pharmacol Ther* **19** (5 (Pt 1)): 531–7.
2. <sup>Δ</sup> Jump up to <sup>Δ</sup>[Hydrochlorothiazide](#). *The American Society of Health-System Pharmacists*. Retrieved Jan 2015.
3. **Jump up**<sup>Δ</sup> Wright, JM; Musini, VM (8 July 2009). "First-line drugs for hypertension.". *The Cochrane database of systematic reviews* (3): CD001841. doi:10.1002/14651858.CD001841.pub2. PMID 19588327.
4. <sup>Δ</sup> Jump up to <sup>Δ</sup><sup>Δ</sup> Duarte JD, Cooper-DeHoff RM (June 2010). "Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics". *Expert Rev Cardiovasc Ther* **8** (6): 793–802. doi:10.1586/erc.10.27. PMC 2904515. PMID 20528637.
5. **Jump up**<sup>Δ</sup> Ravina, Enrique (2011). *The evolution of drug discovery : from traditional medicines to modern drugs* (1 ed.). Weinheim: Wiley-VCH. p. 74. ISBN 9783527326693.
6. **Jump up**<sup>Δ</sup> "WHO Model List of Essential Medicines" (PDF). World Health Organization. October 2013. Retrieved 22 April 2014.
7. **Jump up**<sup>Δ</sup> "Best drugs to treat high blood pressure The least expensive medications may be the best for many people". <http://www.consumerreports.org/>. November 2014. Retrieved 10 January 2015.
8. **Jump up**<sup>Δ</sup> Messerli, Franz; Makani, Harikrishna; Benjo, Alexandre; Romero, Jorge; Alviar, Carlos; Bangalore, Sripal (2011). "Antihypertensive Efficacy of Hydrochlorothiazide as Evaluated by Ambulatory Blood Pressure Monitoring: A Meta-Analysis of Randomized Trials". *J.Am.Coll.Cardiol.* **57** (5): 590–600. doi:10.1016/j.jacc.2010.07.053.
9. **Jump up**<sup>Δ</sup> Mitchell, Deborah. "Long-Term Follow-Up of Patients with Hypoparathyroidism". *J Clin Endocrin Metab. Endocrine Society*. Retrieved 19 June 2013.
10. **Jump up**<sup>Δ</sup> Dvorak MM, De Jossineau C, Carter DH, et al. (2007). "Thiazide diuretics directly induce osteoblast differentiation and mineralized nodule formation by targeting a NaCl cotransporter in bone". *J. Am. Soc. Nephrol.* **18** (9): 2509–16. doi:10.1681/ASN.2007030348. PMC 2216427. PMID 17656470.
11. **Jump up**<sup>Δ</sup> Johnson, KK; Green, DL; Rife, JP; Limon, L (February 2005). "Sulfonamide cross-reactivity: fact or fiction?". *The Annals of pharmacotherapy* **39** (2): 290–301. doi:10.1345/aph.1E350. PMID 15644481.
12. **Jump up**<sup>Δ</sup> Uniformed Services University Pharmacology Note Set #3 2010, Lectures #39 & #40, Eric Marks
13. **Jump up**<sup>Δ</sup> Duarte, JD; Cooper-Dehoff, RM (2010). "Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics". *Expert review of cardiovascular therapy* **8** (6): 793–802. doi:10.1586/erc.10.27. PMC 2904515. PMID 20528637. NIHMSID: NIHMS215063
14. **Jump up**<sup>Δ</sup> "Tour de France: Alexandr Kolobnev positive for banned diuretic". *Velonation*. 2011-07-11. Archived from [the original](#) on 2011-07-12. Retrieved 2011-07-12.
15. **Jump up**<sup>Δ</sup> "Kolobnev denies knowledge of doping product, says not fired by Katusha". *Velonation*. 2011-07-12. Archived from [the original](#) on 2011-07-12. Retrieved 2011-07-12.
16. **Jump up**<sup>Δ</sup> "Press release: Adverse Analytical Finding for Kolobnev". *Union Cycliste Internationale*. 2011-07-11. Archived from [the original](#) on 2011-07-12. Retrieved 2011-07-12.
17. **Jump up**<sup>Δ</sup> "Kolobnev Tour de France's first doping case". *Cycling News* (Bath, UK: Future Publishing Limited). 2011-07-11. Archived from [the original](#) on 2011-07-12. Retrieved 2011-07-12.