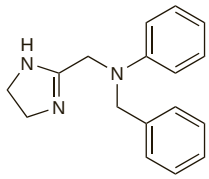
Antazoline *(BAN, rINN)*

Antatsoliini; Antazolin; Antazolina; Antazolinum. *N*-Benzyl-*N*-(2-imidazolin-2-ylmethyl)aniline.

Антазолин

$C_{17}H_{19}N_3$ = 265.4.
CAS — 91-75-8.
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.



Antazoline Hydrochloride *(BANM, rINNM)*

Antatsoliinihydrokloridi; Antazolin hydrochlorid; Antazoline, chlorhydrate d'; Antazolin-hidroklorid; Antazolinhydroklorid; Antazolini Hydrochloricum; Antazolini hydrochloridum; Antazolinium Chloride; Antazolino hidrochloridas; Antazoliny chlorowodorek; Hidrocloruro de antazolina; Imidamine Hydrochloride; Phenazolinum.

Антазолина Гидрохлорид

$C_{17}H_{19}N_3$,HCl = 301.8.
CAS — 2508-72-7.
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Antazoline Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in dichloromethane.

Antazoline Mesilate *(BANM, rINNM)*

Antazoline, Mésilate d'; Antazoline Mesylate; Antazoline Methanesulphonate; Antazolini Mesilas; Antazoliny mezylan; Imidamine Mesylate; Mesilato de antazolina.

Антазолина Мезилат

$C_{17}H_{19}N_3$,CH_3SO_3H = 361.5.
CAS — 3131-32-6.
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.

Pharmacopoeias. In *Pol.*

Antazoline Phosphate *(BANM, rINNM)*

Antazolin Fosfat; Antazoline, Phosphate d'; Antazolini Phosphas; Fosfato de antazolina; Imidamine Phosphate.

Антазолина Фосфат

$C_{17}H_{19}N_3$,H_3PO_4 = 363.3.
CAS — 154-68-7.
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.

Pharmacopoeias. In *US.*
USP 31 (Antazoline Phosphate). A white to off-white crystalline powder. Soluble in water; practically insoluble in ether and in benzene; sparingly soluble in methyl alcohol. pH of a 2% solution in water is between 4.0 and 5.0. Store in airtight containers.

Antazoline Sulfate *(rINNM)*

Antazoline, Sulfate d'; Antazoline Sulphate *(BANM)*; Antazolini Sulfas; Imidamine Sulphate; Sulfato de antazolina.

Антазолина Сульфат

$(C_{17}H_{19}N_3)_2H_2SO_4$,$2H_2O$ = 664.8.
CAS — 24359-81-7 (anhydrous antazoline sulfate).
ATC — R01AC04; R06AX05.
ATC Vet — QR01AC04; QR06AX05.

NOTE. The above molecular formula is that provided in the *It. P.* Other sources give a molecular formula of $C_{17}H_{19}N_3$,H_2SO_4.

Pharmacopoeias. In *It.*

Adverse Effects and Precautions
As for the antihistamines in general, p.561.

Hypersensitivity. Reports of acute interstitial pneumonitis (with fever, rash, and dyspnoea)[1] and of immune thrombocytopenic purpura[2] were attributed to hypersensitivity reactions after the oral use of antazoline.

1. Pahissa A, *et al.* Antazoline-induced allergic pneumonitis. *BMJ* 1979; **2:** 1328.
2. Nielsen JL, *et al.* Immune thrombocytopenia due to antazoline (Antistina). *Allergy* 1981; **36:** 517–19.

Uses and Administration
Antazoline, an ethylenediamine derivative, is an antihistamine used topically for the treatment of allergic conjunctivitis (p.564). It is used as the hydrochloride, phosphate, or sulfate in eye drops, most commonly in a concentration of 0.5%; the mesilate has also been used. Antazoline salts are often used with a vasoconstrictor such as naphazoline hydrochloride or nitrate or xylometazoline hydrochloride.

The hydrochloride and sulfate salts of antazoline have been used topically for the treatment of minor skin irritations, but as with other antihistamines there is a risk of sensitisation. The hydrochloride has also been given by mouth.

Preparations
Proprietary Preparations (details are given in Part 3)

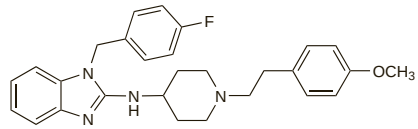
Multi-ingredient: ***Austral.:*** Albalon-A; Antistine-Privine; In A Wink Allergy†; ***Austria:*** Histophtal; ***Belg.:*** Zincfrin Antihistaminicum†; ***Canad.:*** Albalon-A; Vasocon-A†; Zincfrin-A; ***Chile:*** Albasol A†; Bacitopic Compuesto; Nasomin; Oftalirio; Red Off Plus; Rinobanedif; Spersallerg; ***Cz.:*** Sanorin-Analergin; Spersallerg; ***Denm.:*** Ansal; Antistina-Privin; Sesal; ***Fin.:*** Antistin-Privin†; Zincfrin-A†; ***Ger.:*** Allergopos N; Antistin-Privin; Spersallerg; ***Gr.:*** Spersallerg; ***Hong Kong:*** Spersallerg; ***Hung.:*** Spersallerg; ***Indon.:*** Indofrin-A; ***Irl.:*** Otrivine-Antistin; RBC; ***Israel:*** Antistin-Privin†; ***Ital.:*** Antistin-Privina; ***Malaysia:*** Alergoftal; Napha A; Spersallerg; ***Mex.:*** Midazol Ofteno; Oftalirio†; Zincfrin-A; ***Norw.:*** Spersallerg; ***NZ:*** Albalon-A†; Otrivine-Antistin; ***Philipp.:*** Spersallerg; ***Pol.:*** Dermophenazol; Oftophenazol; Rhinophenazol; Spersallerg; ***Port.:*** Alergiftalmina; ***Rus.:*** Sanorin-Analergin (Санорин-аналергин); Spersallerg (Сперсаллерг); ***S.Afr.:*** Albalon-A†; Antistin-Privin; Covosan; Gemini; Oculerge; Safyr Bleu Antihistamine†; Spersallerg; Zincfrin-A; ***Singapore:*** Antistin-Privin; Spersallerg; ***Spain:*** Alergoftal; ***Swed.:*** Antasten-Privin; ***Switz.:*** Antistin-Privin; Spersallerg; ***Thai.:*** Antazallerge; Histaoph; Opsa-His†; Opsil-A; Spersallerg; ***Turk.:*** Alergoftal; Sulfarhin; ***UK:*** Otrivine-Antistin; ***USA:*** Antazoline-V; Vasocon-A.

Astemizole *(BAN, USAN, rINN)*

Astemitsoli; Astemizol; Astemizolas; Astémizole; Astemizolum; Asztemizol; MJD-30. 1-(4-Fluorobenzyl)-2-{[1-(4-methoxyphenethyl)-4-piperidyl]amino}benzimidazole.

Астемизол

$C_{28}H_{31}FN_4O$ = 458.6.
CAS — 68844-77-9.
ATC — R06AX11.
ATC Vet — QR06AX11.



NOTE. The code R-43512 has been used to describe both astemizole and its metabolite tecastemizole (norastemizole).

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Astemizole). A white or almost white powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane and in methyl alcohol. Protect from light.
USP 31 (Astemizole). Store in airtight containers.

Adverse Effects and Precautions
As for the non-sedating antihistamines in general, p.561. Increased appetite and weight gain have been reported with astemizole.

Ventricular arrhythmias, including torsade de pointes, have occurred rarely with astemizole, particularly in association with raised blood concentrations (see Arrhythmias below) and as a result the drug has been withdrawn from the market in most countries. To reduce the risk of developing such arrhythmias recommendations were that licensed doses should **not** be exceeded, and that it should be **avoided** in patients with cardiac or significant hepatic disease, with hypokalaemia or other electrolyte imbalance, or with known or suspected prolonged QT interval. Use with drugs liable to interfere with the hepatic metabolism of astemizole, other potentially arrhythmogenic drugs including those that prolong the QT interval, and drugs likely to cause electrolyte imbalance, is **contra-indicated** (see Interactions below).

Arrhythmias. Although severe life-threatening cardiovascular effects including torsade de pointes and other ventricular arrhythmias were initially reported mainly after substantial overdoses of astemizole, such reactions have also occurred rarely with doses as low as 20 to 30 mg daily and even as low as 10 mg daily in those with possible predisposing factors. There has been a report[1] of astemizole-induced torsade de pointes in a 15-year-old girl who claimed to have taken 10 mg daily for 10 weeks but pharmacokinetic data were more consistent with acute ingestion of higher doses. There have also been several reports of cardiotoxicity after accidental overdosage with astemizole in children.[2-4]

Although the drug is now withdrawn in the UK, recommendations were made by the UK CSM to reduce the risk of developing serious arrhythmias[5-7] (see Adverse Effects above for details). It was considered that astemizole should be stopped immediately in patients who experience syncope, and appropriate clinical evaluation including ECG monitoring instituted, because syncope has preceded or accompanied severe arrhythmias in some cases. Convulsions in patients taking astemizole may also be related to cardiovascular effects.[8]

Studies have suggested that astemizole induces ventricular arrhythmias by inhibiting cardiac potassium channels which results in prolongation of the QT interval, a risk factor for developing arrhythmias.[9] For further discussion, see p.562.

1. Simons FER, *et al.* Astemizole-induced torsade de pointes. *Lancet* 1988; **ii:** 624.
2. Hoppu K, *et al.* Accidental astemizole overdose in young children. *Lancet* 1991; **338:** 538–40.
3. Tobin JR, *et al.* Astemizole-induced cardiac conduction disturbances in a child. *JAMA* 1991; **266:** 2737–40.
4. Wiley JF, *et al.* Cardiotoxic effects of astemizole overdose in children. *J Pediatr* 1992; **120:** 799–802.
5. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
6. CSM/MCA. Drug-induced prolongation of the QT interval. *Current Problems* 1996; **22:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
7. CSM/MCA. Astemizole (Hismanal): only available on prescription. *Current Problems* 1999; **25:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 19/05/06)
8. Clark A, Love H. Astemizole-induced ventricular arrhythmias: an unexpected cause of convulsions. *Int J Cardiol* 1991; **33:** 165–7.
9. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. *Lancet* 1997; **350:** 1115–16.

Overdosage. Severe cardiac events have been associated with astemizole overdosage (see Arrhythmias, above); management is mainly supportive. The absorption of astemizole from the gastrointestinal tract can be prevented by giving activated charcoal[1] but because astemizole is rapidly absorbed it would need to be given as soon as possible after poisoning. Haemodialysis does not appear to increase the clearance of astemizole.

1. Laine K, *et al.* The effect of activated charcoal on the absorption and elimination of astemizole. *Hum Exp Toxicol* 1994; **13:** 502–5.

Porphyria. Astemizole is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Sedation. For discussion of the sedative effects of antihistamines see p.562.

Interactions
As for the non-sedating antihistamines in general, p.563.

Astemizole should not be given with drugs that inhibit its hepatic metabolism because of the increased risk of serious ventricular arrhythmias. These drugs include the imidazole and triazole antifungals such as ketoconazole and itraconazole, and the macrolide antibacterials clarithromycin, erythromycin, troleandomycin, and possibly other macrolides. Others, similarly to terfenadine (p.591), may include serotonin reuptake inhibitors, HIV-protease inhibitors, NNRTIs, and zileuton. The metabolism of astemizole may also be inhibited by grapefruit juice and use together should be avoided.

Use with other potentially arrhythmogenic drugs (including those that prolong the QT interval) such as antiarrhythmics, tricyclic antidepressants, the antimalarials halofantrine and quinine, antipsychotics, cisapride, and the beta blocker sotalol should be avoided, as should diuretics that cause electrolyte imbalances such as hypokalaemia. The use of terfenadine and astemizole together is not recommended.

Pharmacokinetics
Absorption of astemizole from the gastrointestinal tract is rapid and is reduced by food. First-pass metabolism is extensive, therefore plasma concentrations of unchanged drug are very low. The plasma concentration of astemizole plus metabolites takes about 4 to 8 weeks to reach steady state. The metabolism of astemizole is mediated through the cytochrome P450 enzyme system by the isoenzymes CYP3A4, CYP2D6, and CYP2A6. The elimination half-life of astemizole and its metabolites at steady state is about 19 days. Unchanged astemizole is highly bound to plasma proteins and does not appear to cross the blood-brain barrier to a significant extent. Desmethylastemizole, the major metabolite of astemizole, has histamine H_1-receptor-blocking activity; tecastemizole (norastemizole) is another active metabolite. The metabolites of astemizole are excreted slowly in the urine and faeces, and undergo enterohepatic recycling. Virtually none of an oral dose is excreted as unchanged drug.

Uses and Administration
Astemizole, a piperidine derivative, is a non-sedating antihistamine with a very long duration of action. It does not have significant sedative or antimuscarinic actions. Astemizole has been used for the symptomatic relief of allergic conditions including rhinitis (p.565) and conjunctivitis (p.564), and skin disorders such as urticaria (p.565). Preparations of astemizole have now