been reported[5] in renal transplant patients given verapamil and ciclosporin; the authors suggested that if a rapid increase in plasma-ciclosporin concentrations was required, improved formulations of ciclosporin should be used rather than verapamil.

1. Dawidson I, Rooth P. Improvement of cadaver renal transplantation outcomes with verapamil: a review. *Am J Med* 1991; **90** (suppl 5A): 37S–41S.
2. Dawidson I, *et al*. Verapamil improves the outcome after cadaver renal transplantation. *J Am Soc Nephrol* 1991; **2:** 983–90.
3. Chan C, *et al*. A randomized controlled trial of verapamil on cyclosporine nephrotoxicity in heart and lung transplant recipients. *Transplantation* 1997; **63:** 1435–40.
4. Pirsch JD, *et al*. A controlled, double-blind, randomized trial of verapamil and cyclosporine in cadaver renal transplant patients. *Am J Kidney Dis* 1993; **21:** 189–95.
5. Nanni G, *et al*. Increased incidence of infection in verapamil-treated kidney transplant recipients. *Transplant Proc* 2000; **32:** 551–3.

Preparations

BP 2008: Prolonged-release Verapamil Tablets; Verapamil Injection; Verapamil Tablets;
USP 31: Verapamil Hydrochloride Extended-release Tablets; Verapamil Hydrochloride Injection; Verapamil Hydrochloride Oral Solution; Verapamil Hydrochloride Oral Suspension; Verapamil Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Isoptino; Veral; Verapal†; ***Austral.:*** Anpec; Cordilox; Isoptin; Veracaps; Verahexal; ***Austria:*** Isoptin; Verapabene; Verastad; ***Belg.:*** Isoptine; Lodixal; ***Braz.:*** Cordilat; Coronaril; Cronovera†; Dilacard†; Dilacor; Dilacoron; Multicor; Neo Verpamil; Vascord†; Vasoton; Veramil; Veraval; ***Canad.:*** Apo-Verap; Chronovera; Isoptin; Novo-Veramil; Nu-Verap; ***Chile:*** Cardiolen; Isoptina; Presocor; ***Cz.:*** Apo-Verap†; Isoptin; Lekoptin; Verahexal; Verogalid; ***Denm.:*** Geangin; Hexasoptin; Isoptin; Veraloc; ***Fin.:*** Isoptin; Vermin; Verpamil; ***Fr.:*** Isoptine; ***Ger.:*** Azupamil†; durasoptin†; Falicard; Isoptin; Jenapamil†; Vera; Vera-Lich; Verabeta; Veragamma; Verahexal; Veramex; Veranorm; Verasal; Veroptinstada; ***Gr.:*** Brovicarpine†; Elanver†; Isoptin; ***Hong Kong:*** Akilen†; Isoptin; ***Hung.:*** Chinopamil; Isoptin; Verogalid†; ***India:*** Calaptin; Veramil; ***Indon.:*** Cardiover; Isoptin; ***Irl.:*** Isoptin; Veramil; Verap; Verisop; ***Israel:*** Apoacor; Ikacor; Ikapress; Veracor; Verapress; ***Ital.:*** Cardinorm; Isoptin; Kata†; Quasar†; Veraptin; ***Malaysia:*** Akilen; Anpec†; Cintsu†; Isoptin; Verpamil; Viratin†; ***Mex.:*** Cronovera; Dilacoran; Euritmin†; Europave; Serriten; Vepiltax; Veraken; Verdilac; ***Neth.:*** Chronovera†; Geangin; Isoptin; ***Norw.:*** Isoptin; Verakard; ***NZ:*** Civicor†; Isoptin; Verpamil; ***Philipp.:*** Isoptin; Verelan; ***Pol.:*** Isoptin; Lekoptin; Novo-Veramil; Staveran; ***Port.:*** Fibrocard; Isoptin; ***Rus.:*** Finoptin (Финоптин); Isoptin (Изоптин); Lekoptin (Лекоптин); Verogalid (Верогалид); ***S.Afr.:*** Calcicard; Isoptin; Ravamil; Vasomil; Verahexal; ***Singapore:*** Isoptin; Verpamil; ***Spain:*** Manidon; ***Swed.:*** Isoptin; ***Switz.:*** Corpamil†; Flamon; Isoptin; Verapam; ***Thai.:*** Caveril; Civicor†; Isopamil†; Isoptin; Verapin; Vermine; ***Turk.:*** Fibrocard; Isoptin; Ormil; Veroptin; ***UK:*** Cordilox; Half Securon; Securon; Univer; Verapress; Vertab; Zolvera; ***USA:*** Calan; Covera; Isoptin; Verelan; ***Venez.:*** Cronovera; Manidon; Veracor.

Multi-ingredient: ***Arg.:*** Tarka†; ***Austral.:*** Tarka; ***Austria:*** Captocomp; Confit; Tarka; Veracapt; ***Canad.:*** Tarka; ***Cz.:*** Tarka; ***Denm.:*** Tarka; ***Fin.:*** Tarka†; ***Fr.:*** Ocadrik†; Tarka; ***Ger.:*** Cordichin; Isoptin plus; Stenoptin†; Tarka; Udramil†; Veratide; ***Gr.:*** Tarka; Ziaxel; ***Hung.:*** Tarka; ***Indon.:*** Tarka; ***Ital.:*** Tarka; ***Mex.:*** Tarka; ***Neth.:*** Tarka; Ziaxel; ***NZ:*** Ziaxel; ***Philipp.:*** Tarka; ***Pol.:*** Tarka; ***Port.:*** Tarka; Ziaxal; ***Rus.:*** Tarka (Тарка); ***S.Afr.:*** Tarka; ***Spain:*** Tarka; Tricen; ***Swed.:*** Tarka; ***Switz.:*** Tarka; ***Turk.:*** Tarka; ***UK:*** Tarka; ***USA:*** Tarka; ***Venez.:*** Tarka.

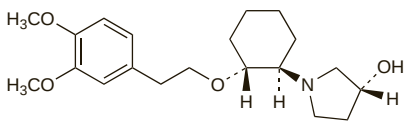
Vernakalant Hydrochloride *(USAN, rINNM)*

Hidrocloruro de vernakalant; RSD-1235; Vernakalant, Chlorhydrate de; Vernakalanti Hydrochloridum. (3*R*)-1-{(1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl}pyrrolidin-3-ol hydrochloride.

Вернаканта Гидрохлорид

$C_{20}H_{31}NO_4$,HCl = 385.9.

CAS — 794466-70-9 (vernakalant); 748810-28-8 (vernakalant hydrochloride).



(vernakalant)

Profile

Vernakalant is an antiarrhythmic under investigation as the hydrochloride for the treatment of atrial arrhythmias.

◊ References.

1. Roy D, *et al*. A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol* 2004; **44:** 2355–61.
2. Fedida D. Vernakalant (RSD1235): a novel, atrial-selective antifibrillatory agent. *Expert Opin Invest Drugs* 2007; **16:** 519–32.
3. Cheng JWM. Vernakalant in the management of atrial fibrillation. *Ann Pharmacother* 2008; **42:** 533–42.

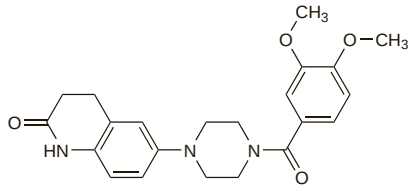
Vesnarinone *(USAN, rINN)*

OPC-8212; Vesnarinona; Vesnarinonum. 1-(1,2,3,4-Tetrahydro-2-oxo-6-quinolyl)-4-veratroylpiperazine.

Веснаринон

$C_{22}H_{25}N_3O_4$ = 395.5.

CAS — 81840-15-5.



Profile

Vesnarinone is a phosphodiesterase inhibitor with positive inotropic activity that has been tried orally in the management of heart failure.

Adverse effects. Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can lead to an increased mortality rate. In a multicentre study of vesnarinone,[1] doses of 120 mg daily resulted in increased mortality whereas 60 mg daily for 6 months was associated with lower morbidity and mortality. Reversible neutropenia occurred in 2.5% of the patients given 60 mg daily. However, in a subsequent larger study,[2] increased mortality was also reported with doses of 30 and 60 mg daily.

1. Feldman AM, *et al*. Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 1993; **329:** 149–55.
2. Cohn JN, *et al*. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med* 1998; **339:** 1810–16.

Warfarin Sodium *(BANM, rINNM)*

Natrii Warfarinum; Sodium Warfarin; Varfariininatrium; Varfarin Sodyum; Varfarino natrio druska; Warfarin sodná sůl; Warfarina sódica; Warfarine sodique; Warfarinnatrium; Warfarin-nátrium; Warfarinum natricum. The sodium salt of 4-hydroxy-3-(3-oxo-1-phenylbutyl)coumarin ; Sodium 2-oxo-3-[(1*RS*)-3-oxo-1-phenylbutyl]-2*H*-1-benzopyran-4-olate.

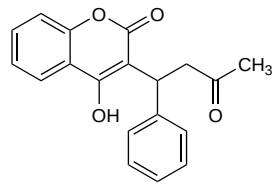
Натрий Варфарин

$C_{19}H_{15}NaO_4$ = 330.3.

CAS — 81-81-2 (warfarin); 2610-86-8 (warfarin potassium); 129-06-6 (warfarin sodium).

ATC — B01AA03.

ATC Vet — QB01AA03.



(warfarin)

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US*.
Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate. *Eur.* has a separate monograph for warfarin sodium clathrate (see below).
Jpn includes Warfarin Potassium.
Ph. Eur. 6.2 (Warfarin Sodium). A white or almost white, hygroscopic, amorphous powder. Very soluble in water and in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.
USP 31 (Warfarin Sodium). A white, odourless, amorphous solid or a crystalline clathrate which is discoloured by light. Very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether. A 1% solution in water has a pH of 7.2 to 8.3. Protect from light.

Adsorption. Studies carried out for periods of 24 hours to 3 months found some adsorption of warfarin sodium by PVC when dissolved in 0.9% sodium chloride solution[1,2] or in 5% glucose solution.[3] In one of these studies,[1] adsorption was decreased by buffering the solution from its initial pH of 6.7 to a pH of 7.4. The second study[2] could demonstrate no adsorption onto polyethylene-lined or glass infusion containers.

1. Kowaluk EA, *et al*. Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; **38:** 1308–14.
2. Martens HJ, *et al*. Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
3. Moorhatch P, Chiou WL. Interactions between drugs and plastic intravenous fluid bags: part i: sorption studies on 17 drugs. *Am J Hosp Pharm* 1974; **31:** 72–8.

Incompatibility. Solutions of warfarin sodium have been reported to be incompatible with adrenaline hydrochloride, amikacin sulfate, metaraminol tartrate, oxytocin, promazine hydrochloride, and tetracycline hydrochloride. Visual incompatibility has been reported[1] with solutions of warfarin sodium mixed with solutions of aminophylline, bretylium tosilate, ceftazidime, cimetidine hydrochloride, ciprofloxacin lactate, dobutamine hydrochloride, esmolol hydrochloride, gentamicin sulfate, labetalol hydrochloride, metronidazole hydrochloride, or vancomycin hydrochloride. Haze was also reported after 24 hours with sodium chloride 0.9%.

1. Bahal SM, *et al*. Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Warfarin Sodium Clathrate *(BANM)*

Varfariininatriumklatraatti; Varfarino natrio druskos klatratas; Warfarin sodná sůl klatrát; Warfarina sódica, clatrato de; Warfarine sodique clathrate; Warfarinnatriumklatrat; Warfarin-nátrium-klatrát; Warfarinum natricum clathratum. The clathrate of warfarin sodium with isopropyl alcohol in the molecular proportions 2 to 1 respectively.

ATC — B01AA03.

ATC Vet — QB01AA03.

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Eur.* (see p.vii).
Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate.
Ph. Eur. 6.2 (Warfarin Sodium Clathrate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.
Warfarin sodium clathrate contains about 92% of warfarin sodium.

Adverse Effects

The major risk from warfarin therapy is of haemorrhage from almost any organ of the body with the consequent effects of haematomas as well as anaemia. Although good control of warfarin anticoagulation is essential in preventing haemorrhage, bleeding has occurred at therapeutic international normalised ratio (INR) values. In such cases the possibility of an underlying cause such as renal or alimentary tract disease should be investigated. Skin necrosis, and purple discoloration of the toes (due to cholesterol embolisation) have occasionally occurred. Hypersensitivity reactions are extremely rare. Other effects not necessarily associated with haemorrhage include alopecia, fever, nausea, vomiting, diarrhoea, skin reactions, jaundice, hepatic dysfunction, and pancreatitis.

Warfarin is a recognised teratogen. Given in the first trimester of pregnancy it can cause a fetal warfarin syndrome or warfarin embryopathy characterised by bone stippling (chondrodysplasia punctata) and nasal hypoplasia. CNS abnormalities may develop after use in any trimester but appear most likely when used in the second or third trimester. Use of warfarin during pregnancy has been associated with an increased rate of abortion and still-birth, although this may, in part, be the consequence of an underlying maternal condition. Use in the late stages of pregnancy is associated with fetal haemorrhage. Reported incidences of the above complications have varied; one estimate is that if a coumarin anticoagulant is taken during pregnancy, one-sixth of pregnancies will result in an abnormal liveborn infant, and one-sixth will result in abortion or stillbirth.

Effects on the blood. The incidence and risk of haemorrhage during long-term oral anticoagulation has been studied in patients in clinical trials[1,2] and in population-based studies.[1,3-7] The risk of bleeding was generally higher with more intense anticoagulation and in the presence of other risk factors, but the relationship with age was less clear. Some studies have shown higher rates of bleeding in elderly patients, but others have not; the risk of intracranial bleeding, however, does seem to be higher in the elderly.[2,6,7] Although cumulative risk of bleeding was related to