

SUMMARY OF DATA FOR CHEMICAL SELECTION

Vincamine 1617-90-9

BASIS OF NOMINATION TO THE NTP

The lack of information on the toxicity of long-term administration of the dietary supplement, vincamine, is brought to the attention of the Chemical Selection Working Group.

This problem first came to the attention of the National Cancer Institute's (NCI) Division of Cancer Biology (DCB) when announcement of the availability of this new dietary supplement was made. Because the information submitted by the company addressed limited studies to show the safety of vincamine use, US Food and Drug Administration (FDA) considers any dietary supplement containing vincamine that is labeled for use by children or for periods in excess of 6 months to be adulterated. However, labeling for short-term use was permitted (FDA 1999; FDA 2000).

The health benefits of vincamine and related compounds, which are sold as drugs in Europe, relate to the treatment of primary degenerative and vascular dementia. As a dietary supplement, vincamine is promoted as a nootropic. The effects of aging are generally chronic, raising concerns about the safety of long-term use of vincamine in its targeted population. Because vincamine is sold as a dietary supplement in the US, the government cannot compel the manufacturer to test the safety of this product.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY:

A CSWG member, Dr. Edwin Matthews, of the Food and Drug Administration (FDA) offered to perform a computational toxicology analysis of vincamine based on the FDA/CDER enhanced MCASE-software developed for FDA by MultiCASE, Inc. This model was employed to predict activities of vincamine and seven structurally related model compounds (brovincamine; eburnamonine; 6-hydroxyvinburnine; reserpine; tacamine; vincanol; and vinpocetine) based on

information available to FDA. Seven endpoints were examined, including carcinogenicity in rodents, teratogenicity in mammals, mutagenicity, adverse liver effects in adult humans, adverse cardiological side effects in adult humans, and adverse kidney side effects in adult humans. Vincamine was predicted to have adverse effect activity on the liver and heart (Matthews, 2003).

SELECTION STATUS: Selected

ACTION BY CSWG: 12/17/02

Studies Requested:

- Genotoxicity assays
- Chromosome aberrations (*in vitro*): compare with vincristine
- 90-day toxicity testing
- Mechanistic studies (sodium pump in brain and heart)

Rationale/Remarks:

- Vincamine was recently approved as a dietary supplement in the US; new dietary supplements receive considerably less scrutiny under Federal law than drugs.
- Existing information supports concerns that this substance may be toxic, especially if doses recommended on the label are exceeded.
- Concerns that vincamine may cause torsade des pointe, a life-threatening arrhythmia, cause this substance to fit within a recent FDA nomination to NTP, *Drugs Positive for QT Interval Prolongation & Proarrhythmia*.

CHEMICAL IDENTIFICATION

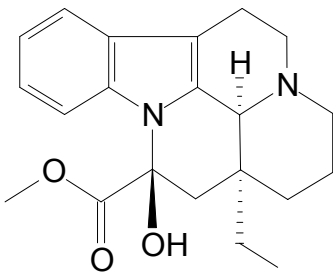
CAS Registry No.

Vincamine, (+)-vincamine, +(<i>cis</i> -vincamine)	1617-90-9
Vincamine hydrochloride	10592-03-7
Vincamine tartrate	64034-84-0
Vincamine teptosilate	51179-28-3

Chemical Abstracts Services Name: Eburnamenine-14-carboxylic acid, 14,15-dihydro-14-hydroxy-, methyl ester, (3 α ,14 β ,16 α)- (9CI)

Synonyms and Trade Name: (+)-Vincamine; Anasclerol; Angiopac; Arteriovinca; Decincan; Devincan; Devinkan; Equipur; methyl vincaminatate; Minorin; Minorine; Monorin; Novicet; Ocuvinc; Oxicebral®; Oxygeron; Perval; Pervincamine; Pervone; Tripervan; Vinca-Ecobi; Vinca-Minor; Vincachron; Vincadar; Vincafolina; Vincamor; Vincagil; vincamidol; vincamin; Vincapan; Vincapront; Vincasaunier; Vincimax; Vinkametrin; Vinodrel retard (ChemID, 2002; Lambert, 1993)

Structure, Molecular Formula, and Molecular Weight:



$C_{21}H_{26}N_2O_3$

Mol. Wt.: 354.44

Structural Class: Indole alkaloid

Chemical and Physical Properties:

Description: Yellow crystals from acetone or methanol (Budavari, 2001)

Principal alkaloid of *Vinca minor* L.; comprises about 25-65% of the indole alkaloids in this plant. Also found in the plant species *Catharanthus roseus*, but should not be

confused with the cytotoxic alkaloids obtained from *Vinca rosea* (Cook & James, 1981; Duke, 2002; Fleming, 2000; Howe-Grant, 1991).

Melting Point: 231.5 °C (Lide, 2000)

Solubility: Sol. in chloroform and methylene chloride, sl. sol. in alcohol and methanol, insol. in water (FDA, 1999)

Technical Products and Impurities: Vincamine (98.0%) is available from Sigma-Aldrich (Sigma-Aldrich, 2002). The Swiss firm, Linnea, a major supplier of botanicals, provides vincamine (≥98.5%) to the dietary supplement industry (Linnea, 2002). Covex also supplies bulk vincamine-related products to the dietary supplement industry (Covex, 2001).

In the US, tablets or capsules containing vincamine are widely available through the various marketing channels for consumer-oriented health-related products, including the Internet (iHerb Inc., 2002; Web Vitamins, 2002). Vincamine is also one of several active ingredients in dietary supplements promoted as “smart drugs” or nootropics (Lambert, 1993). Examples include a vincamine/piracetam combination advertised as a product that "wakes up your brain and focuses your thinking and concentration" and LifeTime® Brain Support formula containing ginkgo biloba extract, huperzine A, vincamine, and phosphatidylserine (InHome Health Services, 2002; Shippy, 2001).

According to the European Agency for the Evaluation of Medicinal Products (EMA), vincamine is mostly used in its hydrochloride and tartrate salt forms (EMA, 1999).

EXPOSURE INFORMATION

Production and Producers:

Manufacturing Process: Vincamine can be extracted from *Vinca minor* directly or by synthesizing it from related Vinca alkaloids. In the process used by Linnea, vincamine is produced through two chemical reactions beginning with the catalytic reduction of tabersonine, an alkaloid extract of Voacanga seeds. The resulting product, vincadiforimine is oxidized forming vincamine (FDA, 1999; Gerhartz, 1985; Linnea, 2002).

Another approach to synthesizing (+)-vincamine uses enamine as the starting material followed by a series of reactions to produce chemical intermediates and finally (+)-vincamine in 78% yield (Szantay, 1999).

Production/Import/Export Level: Vincamine is not listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (ChemID, 2002).

Producers and Importers: Chemical Sources International (2002) lists 7 US suppliers for vincamine.

According to the *OPD Chemical Buyers Directory*, vincamine is manufactured and/or distributed by Bio-Botanica Inc.; Fabrichem, Inc.; Spectrum Chemical Mfg. Corp.; and Westco Fine Ingredients, Inc. (Tilton, 2001).

Use Pattern: Vincamine is an alkaloid obtained from the leaves of *Vinca minor* (*Apocynaceae*) or periwinkle. The periwinkle is a perennial subshrub with evergreen, oval leaves and light blue or violet funnel-shaped flowers. Periwinkle was used during medieval times for headache relief, but vincamine was not identified as the primary component responsible for the plant's medicinal uses until 1953 (EMEA, 1999; Fleming, 2000; Valentine, 1998).

Vincamine is used for the prevention and treatment of cerebrovascular insufficiencies and disorders. It has been shown to be pharmacologically active in the central nervous system and in the cardiovascular system but its activity is mainly on the vessels of the brain. Other therapeutic applications of vincamine include the treatment of tinnitus and hypertension. Vincamine dietary supplements are sold in the US as “brain nutrition” to support cerebral metabolism and cognitive function and to enhance memory and concentration (Healthwell, 2002; iHerb, Inc., 2002; Ritschel & Agrawala, 1985).

Vincamine products are advertised as being able to improve a person’s memory and thinking capacity, mental productivity, and aid in activities requiring focused attention and concentration. These assertions are based on clinical and animal data suggesting that vincamine increases cerebral blood flow, oxygen consumption, and glucose utilization (Blumenthal, 1998; Linnea, 2002; Olpe *et al.*, 1982).

A large body of clinical evidence indicates a favorable effect of vincamine in a number of brain disorders of elderly patients, such as memory disturbances, vertigo, transient ischemic deficits, and headache. The therapeutic efficacy of vincamine administered at 30 mg for 12 wk for treatment of primary degenerative and vascular dementia was demonstrated in a clinical trial involving 152 patients aged 50-85 (Blumenthal, 1998; Fischhof *et al.*, 1996; Olpe *et al.*, 1982).

Human Exposure:

Occupational Exposure: Workers preparing vincamine salts from *Vinca minor* extracts have developed allergic reactions indicating that airborne exposure and dermal contact may occur in this industry (Schmidt, 1984).

No listing for vincamine was found in the National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983.

Consumer Exposure: Consumers are exposed to vincamine through use of dietary supplements containing this substance. The recommended therapeutic dose of vincamine is 40-80 mg daily for at least 20-40 days. To achieve a pharmacological effect, doses must be sufficiently high to reach a plasma concentration of about 0.2 µg/ml. According to the EMEA, this concentration is not achieved from 20 mg administered 3 times a day (EMEA, 1999).

Source Naturals Vincamine, a widely distributed vincamine supplement, is composed of 20 mg tablets with a recommended dosage of one tablet three times a day (iHerb, Inc., 2002). Because of vincamine's very short elimination half-life, sustained release forms are also used (EMEA, 1999). An example is Vincamine retard-ratio-pharm®, a sustained-release tablet containing 30 mg vincamine; dosage is one tablet administered twice daily (Fischhof *et al.*, 1996).

Environmental Occurrence: No information was found in the available literature on potential environmental pollution from the manufacture of vincamine or dietary supplements containing vincamine. *Vinca minor* is indigenous to northern Spain through western France and central and southern Europe, although it has been naturalized in many regions (Fleming, 2000). Contact with vincamine in the environment can occur from individuals using *Vinca minor* as a garden plant (Schmidt, 1984).

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of vincamine. Vincamine was not in the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) and biological exposure index (BEI) are made.

Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). The DSHEA requires no proof of safety for dietary supplements on the market before October 15, 1994. However, vincamine was

not marketed as a dietary supplement in the US at that time. On June 25, 1999, General Nutrition Corporation submitted information to FDA on vincamine pursuant to 21 USC 350b(a)(2). This statute requires manufacturers or distributors of dietary supplements containing a new ingredient to submit the information used to determine safety of the product to FDA at least 75 days before its introduction. FDA concluded that the information submitted was not adequate to conclude that vincamine would be safe for humans under the conditions recommended in the company's label. The company then submitted additional information which led FDA to conclude that sufficient information was now available to provide an adequate basis for the safety of dietary supplements consumed by healthy adults at doses up to 20 mg/day for up to 6 months. However, FDA determined that there was not enough data to establish whether a dietary supplement containing vincamine would be safe for children or for long-term use (FDA, 1999; FDA, 2000).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to vincamine and cancer risk in humans were identified in the available literature.

Animal Data:

Acute Studies: The oral LD₅₀ for vincamine has been reported in rats and mice as shown in Table 1. The vincamine compounds used in these studies were not specified.

Table 1. Acute toxicity values reported for vincamine.

Species	LD ₅₀ (mg/kg bw)	Reference
rat	810	EMEA (1999)
rat	1,200	Sigma-Aldrich (2002)
mouse	825	EMEA (1999)
mouse	460	Sigma-Aldrich (2002)
mouse	1,000	Budavari (2001)

Subacute/Subchronic Studies: Repeated dose toxicity studies in the rat with oral doses of 30 and 100 mg/kg bw/day for 6 weeks and of 6.6, 20, and 62 mg/kg bw/day for 3 months reportedly showed no adverse effects. In the guinea pig, oral doses of 2.5 mg/kg bw for 3 months reportedly showed no adverse effects (EMEA, 1999). No further details were available on these studies.

In dogs, oral administration of vincamine at doses of 1 and 7 mg/kg bw/day for 3 months did not reveal any toxicity. However, at 20 mg/kg bw/day, dogs exhibited behavioral changes. In a second study in Beagle dogs (3 males and 3 females per dose), the α -ketoglutarate salt of vincamine was administered at 0, 3, 11, and 45 mg/kg bw/day (as vincamine) for 91 days. At the highest dose, bilateral testicular atrophy and azoospermia was observed in the males (EMEA, 1999).

Chronic/Carcinogenicity Studies: No 2-year carcinogenicity studies of vincamine were identified in the available literature.

Short-Term Tests:

Vincamine was not mutagenic in a *Salmonella typhimurium* assay for gene mutation with and without S-9 at concentrations of 16-1,500 µg/plate using plate incorporation and at 147-1,500 µg/plate using the preincubation method. Vincamine was also negative for gene mutation in mouse lymphoma cells with and without S-9 at doses of 9.3 -150 µg/ml. Higher concentrations were not used because of solubility limits (EMEA, 1999).

Vincamine did not increase the number of micronucleated polychromatic erythrocytes in the bone marrow of male and female Swiss OF1 mice receiving two oral doses of vincamine at 175, 350, and 700 mg/kg bw/day at 24 hour intervals (EMEA, 1999).

Vincamine has been reported to be a spindle poison; positive in the *Drosophila w/w+* eye mosaic assay (Vogel & Nivard,1993).

Metabolism:

Distribution and Bioavailability: Vincamine is rapidly absorbed. An aqueous solution of 15 mg gives detectable blood levels of >5 ng of unchanged drug/ml for 6 hr. A 30 mg dose given as a slow-release preparation gives similar levels for over 12 hr (Cook & James, 1981).

In volunteers administered aqueous solutions containing 16.9 mg of vincamine hydrochloride or 33.81 mg tablets, the apparent half-life of unchanged vincamine hydrochloride was 30-60 minutes for solutions and 2 hr for tablets. The plasma level was more uniform after administration of the tablet form (Ventouras *et al.*, 1976).

In a crossover study, 6 healthy volunteers received oral doses of 60 mg vincamine pharmaceutical preparations as drops or tablets. Based on calculations using Student's t test, no difference was observed between the maximum plasma concentrations for tablets

and for drops. The peak concentration was observed more slowly with tablets than drops and the AUC was greater with tablets than drops. The authors noted that the short elimination half lives of 1.43 ± 0.80 h with tablets and 1.55 ± 0.78 h with drops would need to be taken into account during chronic administration (Millart *et al.*, 1983).

Although Millart and coworkers described the pharmacokinetic data on orally administered vincamine as fitting a one-compartment model, Seigers and coworkers described two phases of elimination of vincamine after oral administration to humans at doses of 30 or 60 mg (Millart *et al.*, 1983).

Rognoni and coworkers (1977) fitted distribution data in humans to a 7-compartment model based on data from four subjects receiving a single oral dose of vincamine, either 0.7 or 1.4 mg/kg. A high elimination rate through the liver was identified, and the drug was eliminated 2-3 times greater than the transition from blood to the kidney. The reentry from kidney to the blood was projected to be much lower in humans than in rats.

In rats administered 20 mg vincamine (base)/kg bw, a bioavailability of 58% was found with an elimination half-life of 1.71 hours, a t_{max} of 1.27 hours, and a total clearance of 0.818 l/h (higher than the plasma perfusion volume, indicating very quick metabolism in organs in addition to the liver). The amount of unchanged vincamine was 3-11% in the urine and 2-5% in bile. Vincamine was taken up in high concentrations in different organs, resulting in the following ratio: lung/plasma 21, brain/plasma 14.6, kidneys/plasma 14.3, liver/plasma 8.9, and heart/plasma 7.6 (EMEA, 1999).

After oral administration of 20 mg vincamine hydrochloride, bioavailability in dogs ranged between 23 and 58%. After oral administration of 4 mg vincamine hydrochloride/kg bw an elimination half-life of 4.5 hours was observed (EMEA, 1999).

Metabolism: Vigano and colleagues (1978a, 1978b) demonstrated that vincamine is almost completely metabolized in rats after oral administration. The main urinary metabolites were vincamine conjugates.

Radiolabel studies in rats after an oral dose of 10 mg/kg bw demonstrated that vincamine is hydrolysed by the plasma esterases to vincaminic acid which is quickly decarboxylated and oxidized to eburnamenine. Vincamine is also hydroxylated to 6- β -hydroxy-vincamine, which accounts for 40% of the total urinary and biliary radioactivity, followed by 6- α -hydroxyvincamine (8%), and conjugated 6-keto-vincamine (10%). The same hydroxy-keto metabolites could also be detected in the urine of rabbits, dogs, and humans (EMEA, 1999).

Other Biological Effects:

Central Nervous System and Brain: Vincamine hydrochloride, vincamine ketoglutarate, and vincamine teproside prevented the occurrence of cerebral edema and suppressed neurological deficiency caused by the administration of triethyltin hydrochloride in the drinking water of male Wistar rats for 15 days (Borzeix & Cahn, 1984).

According to Benzi and coworkers (1982), the actions of vincamine on catecholamines and serotonin are known. However, these authors sought to determine whether vincamine could interfere with enzymatic activities related to energy transduction in the brains of 6-month old Beagle dogs administered 1, 2, or 3 mg/kg vincamine intravenously (iv) 6 days a week for 12 weeks. The most constant and significant finding was lower activity of acetylcholine esterase in the occipital area, thought by the authors to be related to the extra-mitochondrial redox state.

The action of vincamine on physiological properties of the hippocampal neuronal circuitry, a structure thought to be involved in processes related to memory and learning, has been measured. Although a five-minute perfusion of vincamine at 100 μ M did not affect the excitability of the pyramidal neurons in hippocampal slice preparations, this dose significantly reduced the post-tetanic and long-term potentiation evoked by repetitive stimulation of the Schaffer-coissural fiber system (Olpe *et al.*, 1982).

Cognitive Function: In humans, seven double-blind studies in the German literature with vincamine reported improved scores on some psychometric tests in treated patients (Cook & James, 1981).

Vincamine did not increase acquisition of the avoidance response in male Wistar-derived spontaneously hypertensive rats, but proved effective in the prevention of a hypoxia-induced learning deficit when administered orally at 20 mg/kg 60 minutes before testing (Groo *et al.*, 1988). Vincamine also showed a favorable effect on reversal of amnesia and recall in mice impaired by scopolamine (Groo *et al.*, 1987). Vincamine has been reported to be a potent blocker of voltage-gated Na⁺ channels (Erdö *et al.*, 1996).

Heart Rate/Blood Pressure/Blood Flow: Both vincamine and ethyl apovincamate have been shown to lower blood pressure and increase heart rate in animals (Cook & James, 1981).

Several studies have reported an increase in mean cerebral blood flow after iv infusion of 30-40 mg of vincamine in patients with cerebrovascular disease. Another study found no effect at 30 mg iv but demonstrated a slight increase in blood flow in patients given 40 mg iv. No reliable studies of blood flow after oral medication were found (Cook & James, 1981).

Vincamine hydrochloride had a vasodilatory effect on small arteries in rats. This activity was found to be 0.27 times of the activity observed for papaverine hydrochloride (Piacenza and Pesce, 1978).

Torsade des Pointe: Tachycardias that arise in the lower chambers (known as "ventricular tachycardia") often result in sudden loss of consciousness and can cause sudden death. These tachycardias are most often seen in patients who have had heart attacks, even in those patients who may have had the heart attack months or years prior to the tachycardia. Ventricular tachycardias are also seen in patients who have cardiomyopathy. A very unusual condition that can result in ventricular tachycardia, often referred to as "torsade des

pointe" is associated with abnormal recovery of the heart muscle after contraction called "idiopathic long QT syndrome." The latter condition runs in families, can be associated with deafness, results in blackout spells and can be lethal. Torsade can also be caused by some medications (Gomes, 2001).

Several European case reports have associated torsade des pointe with administration of vincamine where vincamine and ethyl apovincamate have been used extensively as cerebral vasodilators (see, for example, Dany *et al.*, 1979).

In Italy, an 83 year-old woman developed a long QT syndrome followed by torsade des pointe following administration of prenylamine, vincamine, digitalis, and furosemide (Fanelli *et al.*, 1979).

In France, six patients developed ventricular arrhythmias following parenteral or intramuscular administration of vincamine. Five had recorded attacks of torsade des pointe, which recurred in one following readministration of vincamine. One patient had syncope. Although an ECG was not recorded at the time, a follow-up ECG showed a long QT interval and R/T ventricular extra systoles. Symptoms were generally neurological, with syncope, cyanosis, and convulsions. Three patients showed spontaneous regression of symptoms, but in the others, vincamine administration had to be stopped and cardiopulmonary resuscitation instituted (Dany *et al.*, 1979).

In a followup study, Dany and colleagues (1981) described a seventh case of ventricular arrhythmia following injection of vincamine.

Liver Toxicity: In an evaluation of vincamine and vindeburnol, an eburnamenine derivative that has occasionally shown hepatotoxic properties in humans, five groups of 10 male Sprague-Dawley rats per group received 30-120 mg/kg/day of vindeburnol, 120 mg/kg/day of vincamine, or vehicle (1% carboxymethyl cellulose) per os for six days. No significant differences in blood markers of liver damage (aminotransferases, alkaline phosphatase and

γ -glutamyl transpeptidase activities, bilirubin, α_1 -acid glycoprotein and albumin levels) were observed from vincamine administration (Porquet *et al.*, 1992).

In white male NMRI mice, liver tissues were examined 1, 4, 8, and 24 hr or 7 days after a single intraperitoneal dose of 0.5 mg vincamine. Thin sections examined by electron microscopy showed hepatic parenchymal cells ranging from normally structured to mildly damaged. Slightly enlarged mitochondria, also increased in number, were conspicuous, and Kupffer cells were activated and exhibited a high degree of phagocytic activity. Numerous bile canaliculi showed dilatation of the lumen and a reduction in or complete absence of microvilli (Rassat *et al.*, 1982).

More significant changes were evident using a freeze-fracture method. The zonulae occludentes (tight junctions) of the liver normally appear in freeze-fracture replicas as a well-organized network of branching and interconnecting ridges with complementary grooves. Livers from vincamine-treated mice showed a high degree of change. The bile canaliculus lumen was dilated and the margins irregular in outline. Corresponding tight junctions of the zonulae occludentes showed an irregular outline with numerous free-ending strands on the lateral surface of the plasmalemma. The network of the zonulae occludentes as a whole appeared loosened and disordered. In numerous regions of the plasmalemma, a heavy proliferation of tight junctions was observed. This well-defined network was intermeshed with the zonulae occludentes, or alternatively, isolated tight junctional complexes were observed on the lateral plane of the plasmalemma. These junctional complexes exhibited no connections with the pericanalicular zonula occludens. In some instances, the tight junctional configuration showed interconnections with gap junctions. There were also alterations in the gap junctions located between the bile canaliculi and the space of Dissé. The gap junctions in livers treated with vincamine showed a high degree of change, being enlarged and exhibiting a lobular outline with numerous particle evaginations on the plasmalemma. A prominent feature was the increase of gap junctions, a great number occupying areas in a small region of plasma membrane (Rassat *et al.*, 1982).

Reproductive Toxicity: As described previously, vincamine produced testicular atrophy and azoospermia in Beagle dogs at 45 mg/kg bw/day for 91 days. In rats administered 0-37.5 mg/kg bw/day of vincamine (as the α -ketoglutarate) from day 6 to 16 of gestation, the 7.5 mg/kg dose caused an increase in the number of placental hemorrhages. A dose of 22.5 mg/kg induced a reduction of fertility, loss of maternal body weight, fewer fetuses, smaller and lighter fetuses, and marked delay in ossification of fetuses. Only one fetus of 6 gravid females was recorded at the 37.5 mg/kg dose. Administration of 225 mg/kg bw/day by the oral route had no effect on the reproductive function in male rats. In mice (30 animals per group) administered 50 mg vincamine/kg bw/day by stomach tube one week before mating until sacrifice or birth, fetal resorption was increased. Fertility was also significantly diminished in rabbits receiving iv administration of vincamine (EMEA, 1999).

Contact Sensitivity: A case study of a 39-year old man with acute eczematous contact dermatitis of the eyelids and neck attributed to exposure to vincamine tartrate during work in a pharmaceutical firm was reported. Sensitivity to vincamine was confirmed by patch testing with a 1% solution of vincamine tartrate. This communication further describes an earlier study in which 11 patch tests positive for sensitivity to Vinca alkaloids were found among 18 of 48 workers with contact dermatitis. Cross-sensitivity to Rauwolfia alkaloids was also observed (van Hecke, 1981).

Respiration: Continuous iv perfusion of vincamine hydrochloride increased pulmonary resistance due to direct contraction of the tracheo-bronchial smooth muscles on respiratory parameters were studied *in vitro* on five isolated guinea pig tracheas and *in vivo* in four dogs. (Piacenza *et al.*, 1978).

Structure-Activity Relationships:

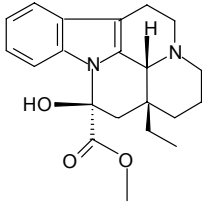
Although vincamine is sold in the US as a dietary supplement, several closely related compounds are drugs used for the same purpose as vincamine. These include vinpocetin and vincamine 2-oxoglutarate, among others. Vincamine also has some structural and pharmacologic similarities to reserpine (Cook & James, 1981). Vinpocetine, a cerebral

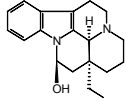
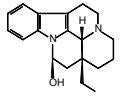
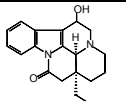
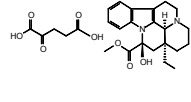
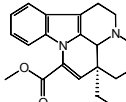
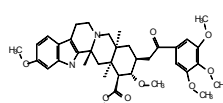
activator reported to prevent memory impairment in mice, did not antagonize reserpine-induced ptosis or catalepsy in standardized rodent tests (Keim & Hall, 1987).

Ethyl apovincamate is sold commercially as the drug, Cavinton®. When Cavinton® was administered by intratracheal intubation for six months to rats (25-100 mg/kg/day), mild tubular degeneration was seen at 50 mg/kg doses (but not at 100 mg/kg) and mild, reversible functional plasmatic and nuclear changes characterized by minor extra and intracellular swelling were observed in the liver. In dogs administered Cavinton® for six months (5 and 25 mg/kg daily doses), liver and kidney function was not impaired and histological results did not reveal systemic toxicity (Cholnoky and Dömök, 1976).

Information from the Toxnet databases was gathered on the carcinogenicity and mutagenicity of six compounds structurally related to vincamine (as determined by ChemID criteria using 80% similarity). No information on the other alkaloids was found in a search of the available literature. Reserpine was positive in three out of four species/sex combinations when tested by the NTP, and some human data suggests it may induce breast cancer. Notwithstanding, this substance has been consistently negative in genotoxicity /mutagenicity tests. This information is presented in Table 2 below.

Table 2. Data on the carcinogenicity and mutagenicity of substances structurally related to vincamine

Name/CAS No.	Structure	Use	Information on Carcinogenicity & Mutagenicity
Vincamine 1617-90-9	 <p>The chemical structure of Vincamine is a complex polycyclic alkaloid. It features a central indole-like ring system fused to a piperidine ring, which is further fused to a decalin-like system. A hydroxyl group (HO) is attached to one of the bridgehead carbons, and an ethyl ester group (O-C(=O)-CH2-CH3) is attached to another bridgehead carbon. The structure is shown with stereochemistry indicated by wedges and dashes.</p>	Dietary supplement /nootropic Used in Europe as Oxicebral®	Spindle poison; positive in <i>Drosophila</i> w/w ⁺ eye mosaic assay (Vogel & Nivard,1993) Negative in the Ames assay, the micronucleus test, and in the mouse lymphoma assay (EMEA, 1999)

Vincanol 19877-89-5		Drug/therapeutic agent (ChemID, 2002)	No information found in Toxnet
Eburnamine 473-99-4			No information found in Toxnet
6-Hydroxy- vinburnine 101242-46-0			No information found in Toxnet
Vincamine 2- oxoglutarate 54341-01-4		Anticoagulants; drug/therapeutic agent (ChemID, 2002) Oxovinca®	No information found in Toxnet
Vinpocetine 42971-09-5		Drug/therapeutic; reproductive effect (ChemID, 2002) Cavinton®	No information found in Toxnet
Reserpine 50-55-5		Adrenergic uptake inhibitors; antihypertensive agents; antipsychotic agents; drug/ therapeutic agent; human data; mutation data; reproductive effect; sympatholytics; tumor data Many trade names	Reasonably anticipated to be a carcinogen (ChemID, 2002) Early retrospective studies implicated reserpine in breast cancer, but data from prospective studies and meta- analysis of several case -controlled studies show only a weak association (Grossman <i>et</i> <i>al.</i> , 2002) In NCI/NTP study (diet, 2 yr), positive in female mice (mammary gland), male mice (seminal vesicles),

			<p>and male rats (adrenal gland) (CCRIS, 2002)</p> <p><i>Salmonella typhimurium</i> TA97, TA98, TA100 & TA1535 with/without S-9: Negative (CCRIS, 2002)</p> <p><i>E. coli</i> wp2 Uvra with/without S-9: Negative (CCRIS, 2002)</p> <p>UDS rat hepatocytes: Negative (CCRIS, 2002)</p>
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References

- Benzi, G., Arrigoni, E., Pastoris, O., Marzatico, F., Curti, D. Et al. (1982) *Farmaco Ed. Sci.*, **36**(Sept), 811-816
- Blumenthal, M., ed. (1998) *The Complete German Commission E Monographs*. Boston, MA, American Botanical Council, pp. 364-365
- Borzeix, M.G. & Cahn, J. (1984) Cerebral antiedematous effect of Teproside and of some vincamine derivatives. *Int. J. Clin. Pharmacol. Res.*, **4**(4), 259-261
- Budavari, S., ed. (2001) *The Merck Index*, 13th ed., Whitehouse Station, NJ, Merck & Co., Inc., p. 1778-79
- CCRIS (2002) Reserpine. *Chemical Carcinogenesis Research Information System (CCRIS)*, National Library of Medicine Toxnet database. Record: 550. [<http://toxnet.nlm.nih.gov>]. Searched November 21, 2002
- Chemical Sources International (2002) *All Chemical Suppliers for: Vincamine and Vincamine Hydrochloride*. [<http://db.chemsources.com/chemsources/>]. Searched November 11, 2002
- ChemID (2002) Chemical Identification. [Record nos. 50555; 473994; 19877895; 42971095; 101242460; 1617909; 54341014]. National Library of Medicine, Bethesda, MD. [<http://chem.sis.nlm.nih.gov/chemid/>]. Searched November 21, 2002
- Cholnoky, E. & Doemoek, L.I. (1976) Summary of safety tests of ethyl apovincamate. *Arzneim. Forsch.*, **26**, 1938-1944
- Cook, P. & James, I. (1981) Cerebral vasodilators. *N. Engl. J. Med.*, **305**(26), 1560-1564
- Covex (2001) *Got Brain? Vinpocetine, Intellectol, Memory Pill, Mind, Vitamin, Supplements*. [<http://www.intellectol.com/raw.html>]. Searched August 2, 2001
- Dany, F., Merle, L., Goudoud, J.C., Liozon, F., Blanc, P., Bouvot, J.C., Nicot, G. & Dangoumau, J. (1981) Cardiac toxicity of vincamine: a seven cases report of ventricular arrhythmias by parenteral administration of vincamine. *Therapie*, **36**(1), 55-64 [French]
- Dany, F., Liozon, G., Goudoud, J.C., Castel, J.P., Michel, J.P., Marsaud, P., Merle, L. & Dallochio, M. (1980) Severe ventricular arrhythmia following parenteral administration of vincamine. Predisposing factors in 6 cases. *Arch. Mal. Coeur Vaiss.*, **73**(3), 298-306 [French]
- Duke, J.(2002) Agriculture Research Service, National Genetic Resources Program. *Phytochemical and Ethnobotanical Databases*. National Germplasm Resources Laboratory, United States Department of Agriculture Beltsville, Maryland. [<http://sun.ars-grin.gov:8080/npgspub/xsql/duke/listchem.xsql>]. Searched on November 8, 2002

Erdő, S.L., Moolná, P., Lakics, V., Bence, J.Zs, & Tömösközi, Z. (1996) Vincamine and vincanol are potent blockers of voltage-gated Na⁺ channels. *Eur. J. Pharmacol.*, 314(1-2), 69-73 [abstract].

EMA (1999) *Committee for Veterinary Medicinal Products Vincamine Summary Report*. Document EMA/MRL/587/99-FINAL. European Agency for the Evaluation of Medicinal Products (EMA), Veterinary Medicines Evaluation Unit [<http://www.emea.eu.int/pdfs/vet/mrls/058799en.pdf>]. Searched November 18, 2002

Fanelli, R., Piemontese, M., Di Michele, M., & De Matteis, D. (1979) Verapamil and torsade de pointe. *G. Ital. Cardiol.*, 9(9), 1028-1029 [Italian]

FDA (1999) *75-Day Premarket Notification for New Dietary Ingredient Vincamine* submitted by General Nutrition Corporation to the Food and Drug Administration, Dockets Management Branch, 11 pp

FDA (2000) *75-Day Premarket Notification for New Dietary Ingredient Vincamine* submitted by General Nutrition Corporation to the Food and Drug Administration, Dockets Management Branch, 7 pp

Fischhof, P.K., Moslinger-Gehmayr, R., Herrmann, W.M., Friedmann, A. & Russmann, D.L. (1996) Therapeutic efficacy of vincamine in dementia. *Neuropsychobiology*, 34(1), 29-35

Fleming, T., ed. (2000) *PDR for Herbal Medicines*, 2nd ed., Montvale, NJ, Medical Economics Company, p 584-5

Gerhartz, W., ed. (1985) *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed., Deerfield Beach, FL, VCH Publishers, p 393

Gomes, J.A. (2001) Condition summary: Tachycardia. *Health Information*. [<http://bestdoctors.com/>]. Searched November 21, 2002

Groo, D., Palosi, E. & Szporny, L. (1988) Comparison of the effects of vinpocetine, vincamine, and nicergoline on the normal and hypoxia damaged learning process in spontaneously hypertensive rats. *Drug Dev. Res.*, 15(1), 75-85

Groo, D., Palosi, E. & Szporny, L. (1987) Effects of vinpocetine in scopolamine induced learning and memory impairments. *Drug Dev. Res.*, 11(1), 29-36

Grossman, E., Messerli, F.H., Goldbourt, U. (2002) Carcinogenicity of antihypertensive therapy. *Curr. Hypertens. Rep.*, 4(3), 195-201

Healthwell (2002) Tinnitus. *Vincamine Search Results*. [<http://www.healthwell.com>]. Searched November 19, 2002

- Howe-Grant, M., ed. (1991) *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed., New York, NY, John Wiley & Sons, p 1073
- Hutter, K., Deli, L. & Csomos, I. (1980) Successful resuscitation from sudden death caused by Cavinton. *Orv. Hetil.* Feb 17, **121**(7), 397-398 [Hungarian]
- iHerb Inc. (2002) Brain Nutrition, Source Naturals. [<http://www.iherb.com/brainnutrition1.html>]. Searched November 21, 2002
- InHome Health Services (2002) *Anacervix product listing*. [<http://www.inhome-health.com>] Searched November 15, 2002
- Keim, K.L., & Hall, P.C. (1987) General neuropharmacology of vinpocetine: putative cerebral activator. *Drug Dev. Res.*, **11**(2), 107-115
- Lambert, V. (1993) Using smart drugs and drinks may not be smart. *FDA Consumer*. April, 24-26
- Lide, D.R., ed. (2000) *CRC Handbook of Chemistry and Physics*, 80th ed., (On CD-Rom), Boca Raton, FL, CRC Press
- Linnea (2002) *Vincamine Search Results*. [<http://www.linnea-worldwide.com>]. Searched November 15, 2002
- Manconi, E., Binaghi, F. & Pitzus, F. (1986) Double blind clinical trial of vinpocetine in the treatment of cerebral insufficiency of vascular and degenerative origin. *Curr. Ther. Res.*, **40**(Oct.) 702-709
- Matthews, E. (2003) Personal communication from Dr. Edwin Matthews, Food and Drug Administration, to Dr. Jean Sevin, Technical Resources International, Inc., 1/13/03
- Millart, H., Lamiable, D., Houin, G., Plat, M., Choisy, H. & Tillement, J.P.(1983) Pharmacokinetic study of two pharmaceutical preparations containing alkaloid vincamine administered orally to human subjects. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **21**(11), 581-586
- Olpe, H.R., Barrionuevo, G. & Lynch, G. (1982) Vincamine: a psychogeriatric agent blocking synaptic potentiation in hippocampus. *Life Sci.*, **31**(18), 1947-1953
- Piacenza, G. & Pesce, E. (1978) Effects of vincamine on the mesenteric circulation in the rat *Farmaco Ed. Prat.*, **33**, 326-332 [Italian] (Abstract)
- Piacenza, G. Pesce, E. & Marchini, F. (1978) Respiratory effects of vincamine hydrochloride. *Farmaco Ed. Prat.*, **33**, 319-325 [Italian] (Abstract)
- Porquet, D., Appel, M., Fournier, T., Bertaux, O., Biou, D. & Féger, J. (1992) Evaluation of the hepatotoxicological effects of a drug in an *in vivo/in vitro* model. *Experientia*, **48**, 257-261

- Rassat, J., Robenek, H. & Themann, H. (1982) Changes in mouse hepatocytes caused by vincamin. A thin-sectioning and freeze-fracture study. *Naunyn Schmiedebergs Arch. Pharmacol.*, **318**(4), 349-357
- Ritschel, W.A. & Agrawala, P. (1985) Biopharmaceutic and pharmacokinetic aspects of vincamine HCl. *Methods Find Exp. Clin. Pharmacol.*, **7**(3), 129-136
- Rognoni, F., Vigano, V., Periti, P. & Colombo Pirola, L. (1977) Multicompartmental modeling and kinetic parameter identification of the systemic distribution of vincamine after oral administration in the rat and in the man. *Int. J. Clin. Pharmacol. Biopharm.*, **15** (Aug), 373-380
- Schmidt, R.J. (1984) Apocynaceae (Dogbane family). *Botanical Dermatology Database*. [<http://bodd.cf.ac.uk/BoDDHomePage.html>]. Searched November 15, 2002
- Shippy, H.A. (2001) Personal communication [letter] from Harry August Shippy, President, Nutritional Specialties, Inc., Anaheim, CA, to Office of Special Nutritionals, Center for Food Safety and Applied Nutrition, FDA, Washington, DC, January 2, 2001
- Siegers, C.P., Iven, H. & Strubelt, O., (1977a) Plasmaspiegel und renale Ausscheidung von Vincamin oraler Applikation bei Probanden. *Arzneim. Forsch./Drug Res.*, **27**(I), 1271-1274 (cited in Millart *et al.*, 1983)
- Siegers, C.P., Heib, W.D. & Kohlmeyer, K. (1977b) Plasma und Liquor-spiegel von Vincamin nach intravenöser Infusion bei Patienten. *Arzneim. Forsch./Drug Res.*, **27**(I), 1274-1277 (cited in Millart *et al.*, 1983)
- Sigma-Aldrich (2002) Vincamine. *Search Results*. [<http://www.sigmaaldrich.com>]. Searched November 11, 2002
- Spagnoli, A. & Tognoni, G. (1983) "Cerebroactive" drugs. Clinical pharmacology and therapeutic role in cerebrovascular disorders. *Drugs*, **26**(1), 44-69
- Szántay, C. (1999) Resolution, chiral synthesis or what? Studies in alkaloid chemistry. *Pure Appl. Chem.*, **71**(6), 1105-1108
- Tilton, H., ed. (2001) *OPD Chemical Buyers Directory*. New York, NY, Schnell Publishing
- Valentine, R. (1998) Herbs offer hope for your headache. *Delicious*, Issue 01/98
- van Hecke, E. (1981) Contact sensitivity to vincamine tartrate. *Contact Dermatitis*, **7**(1), 53
- Ventouras, K., Schulz, P., Doelker, E., Boucherat, J. & Buri, P. (1976) Pharmacokinetic study of vincamine administered orally. *Pharm. Acta Helv.*, **51**(11), 334-342 [French] (Abstract)

Vigano, V., Paracchini, S., Piacenza, G. & Pesce, E. (1978a) Metabolism of vincamine in the rat. *Farmaco [Sci.]*, **33**(8), 343-350 [Italian]

Vigano, V., Rognoni, F., Piacenza, G. & Pesce, E. (1978b) Absorption, distribution and elimination of vincamine hydrochloride in the rat. *Farmaco [Sci.]*, **33**(5), 224-231 [Italian]

Vogel, E.W. & Nivard, M.J.(1993) Performance of 181 chemicals in a *Drosophila* assay predominantly monitoring interchromosomal mitotic recombination. *Mutagenesis*, **8**(1), 57-81

Web Vitamins (2002) Vincamine. *Search Results*. [<http://www.webvitamins.com>] Searched November 18, 2002