

The different names used for trientine and triethylenetetramine

Some chemistry of triethylenetetramine (trientine)

In chemistry, a **salt** is formed when an **acid** is mixed with an equivalent amount of a **base**, usually in aqueous solution. For example, by mixing dilute hydrochloric acid with the correct proportion of aqueous sodium hydroxide (a base), sodium chloride (common salt) is formed and may be isolated by evaporating off the water.

Triethylenetetramine is also a base which on mixing with hydrochloric acid (HCl) in water can produce two salts depending on the amount of HCl added. The first salt produced is **triethylenetetramine dihydrochloride**. By adding further amounts of HCl the dihydrochloride is converted into a second salt, **triethylenetetramine tetrahydrochloride**. Both salts may be isolated as crystalline solids by evaporating the two respective aqueous solutions under reduced pressure [di = two; tetra = four].

A better understanding of these two salts comes from looking at the chemical structure of triethylenetetramine: $\text{H}_2\text{NCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2$. This compound contains four nitrogen atoms (N) (shown in red). The rest of the molecule consists of six carbon atoms and eighteen hydrogen atoms (C and H). In the dihydrochloride the two terminal nitrogen atoms interact with HCl; in the tetrahydrochloride, all four nitrogen atoms interact with HCl. A unique property of triethylenetetramine is that the four nitrogen atoms can wrap around copper (as cupric ions) to form a chelate. In the jargon of chemistry, triethylenetetramine complexes with cupric ions to form a chelate (also called a coordination compound). It is this property that allows triethylenetetramine to be used so effectively for treating Wilson's disease.

Triethylenetetramine base is a liquid. It is more convenient to administer a (solid) salt of triethylenetetramine to patients. Since its introduction by Dr John Walshe in 1969, **triethylenetetramine dihydrochloride** has been used to treat Wilson's disease. Recently (2018) a French company GMP-Orphan SAS has initiated clinical trials of **triethylenetetramine tetrahydrochloride** for the treatment of Wilson's disease. Therapeutically, both the dihydrochloride and the tetrahydrochloride salts revert to the free base, triethylenetetramine, in the body. With copper, the resulting triethylenetetramine–copper chelate is then excreted in the patient's urine thus reducing the overall body burden of copper in patients with Wilson's disease.

The different names used for triethylenetetramine dihydrochloride and triethylenetetramine

Rather than the common chemical name, triethylenetetramine, the generic name **trientine** has been adopted when **triethylenetetramine** is used as a drug. Trientine's copper chelating properties have also been investigated for the treatment of diseases unrelated to Wilson's disease. As a result, **triethylenetetramine dihydrochloride** has acquired a number of approved, colloquial, trade and code names. There are two (generic) Approved Names for this drug: **trientine dihydrochloride**, which is the British Approved Name (BAN) and the World Health Organization (WHO) International Nonproprietary Name (INN) and **trientine hydrochloride**, which is the United States Adopted Name (USAN). These two names refer to the same product – **trientine dihydrochloride**.

Pharmaceutical manufacturers/traders who provide trientine dihydrochloride for patients each use a different trade name for the drug. Trade names used by four companies which supply trientine dihydrochloride are shown in the Table below.

Table: Some trade names used for trientine dihydrochloride

Trade name	Company/country	Trientine dihydrochloride content/capsule (mg)	Trientine free base/capsule (mg)	Principal region(s) supplied
Syprine [†]	Bausch Health Companies/USA	250	167	USA
Cufence	Univar Solutions B.V./The Netherlands	300	200	Europe [‡]
Metalite	Tsumura/Japan	250	167	Japan
Cuchel	MSN Laboratories/India	250	167	India

[†] Syprine is available from other USA companies listed on the website <https://www.drugs.com/availability/generic-syprine.html> (accessed 9th September 2019).

[‡] At present (2019) Univar markets trientine dihydrochloride in the UK under its generic name.

Other brand and code names for trientine which appear in the literature and on the web include Cuprid (Merck); Laszarin (Protemix); MK-681; PX 811019 (Protemix); KD034 (Kadmon). Merck is a USA pharmaceutical company, which relinquished its interests in trientine in 2004, ProteMix a former New Zealand biotech company, and Kadmon a USA company. Trientine is wrongly spelt 'trientene' in several scientific papers, which may be found from a Google Scholar search.

As mentioned above, trientine dihydrochloride and trientine tetrahydrochloride are prepared from triethylenetetramine. Triethylenetetramine itself has multiple applications, and also has acquired many different chemical names and code names, which are often used in the chemical literature: triethylenetetramine; *N,N'*-bis(2-aminoethyl)-1,2-ethanediamine; 1,8-diamino-3,6-diazaoctane; 3,6-diaza-1,8-octanediamine; 1,4,7,10-tetraazadecane; trien; TETA. All these names refer to the same substance, triethylenetetramine (the free base).

Cufence 200 mg capsules

In May 2019, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) granted marketing authorisation for Univar's **trientine dihydrochloride**. This decision will facilitate the availability of trientine dihydrochloride in the European Union. As part of its application for EMA recognition, Univar has adopted the trade name **Cufence** for trientine dihydrochloride. Cufence capsules will be labelled 'Cufence capsules 200 mg'. The '200 mg' refers to the amount of trientine (triethylenetetramine) base in each capsule. In the UK, these same capsules are labelled 'trientine dihydrochloride capsules 300 mg'. The '300 mg' refers to the amount of trientine dihydrochloride in each capsule. The explanation of these two different amounts is as follows:

The molecular formula of trientine base (triethylenetetramine) is $C_6H_{18}N_4$ which has a molar mass 146.2 grams/mole [the sum of the atomic masses of 6 x carbon atoms, 18 x hydrogen atoms and 4 x nitrogen atoms]. The molecular formula of trientine dihydrochloride is $C_6H_{18}N_4 \cdot 2HCl$ which has a molar mass 219.2 grams/mole. One mole (146.2 g) of trientine base is equivalent to one mole (219.2 g) of trientine dihydrochloride. Hence $200 \text{ mg trientine base} = (219.2 \div 146.2) \times 200 = 300 \text{ mg trientine dihydrochloride}$.

Cuprior 150 mg tablets

The trade name for **trientine tetrahydrochloride** chosen by GMP-Orphan SAS is **Cuprior**, which will be marketed as film-coated tablets each containing the equivalent of 150 mg trientine free base.

Rupert Purchase, March 2017; revised and updated June 2019 and September 2019