

**Incompatibility and stability.** The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, below.

### Sodium Sulfite

Anhydrous Sodium Sulphite; E221; Exsiccated Sodium Sulphite; Natrii Sulfis; Natrii sulfis anhydricus; Natrii Sulfis Siccatus; Natrii Sulphis; Natrio sulfitas, bevandenis; Natriumsulfitti, vedetön; Natriumsulfitt, vattenfritt; Siñžitan sodný; Sodium (sulfite de) anhydre; Sodium Sulphite; Sodu siarczyn; Sulfito sódico; Vízmentes nátrium-szulfitt.

$\text{Na}_2\text{SO}_3 = 126.0$ .  
CAS — 7757-83-7.

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), and *Jpn.* Also in *USNF*.

*Eur.* also includes the heptahydrate.

**Ph. Eur. 6.2** (Sodium Sulphite, Anhydrous; Natri Sulfis Anhydricus). A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol. Store in airtight containers.

**Ph. Eur. 6.2** (Sodium Sulphite Heptahydrate; Natrii Sulfis Heptahydricus). Colourless crystals. Freely soluble in water; very slightly soluble in alcohol.

**USNF 26** (Sodium Sulfite). Colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Store in airtight containers.

**Incompatibility and stability.** The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, below.

### Sulfur Dioxide

Dióxido de azufre; E220; Kükürt Dioksit; Siarki dwutlenek; Sulphur Dioxide.

$\text{SO}_2 = 64.06$ .  
CAS — 7446-09-5.

**Pharmacopoeias.** In *USNF*.

**USNF 26** (Sulfur Dioxide). A colourless non-flammable gas with a strong suffocating odour characteristic of burning sulfur. It condenses readily under pressure to a colourless liquid that boils at  $-10^\circ$  and has a wt per mL of about 1.5 g. Soluble 36 in 1 of water and 114 in 1 of alcohol by vol. at  $20^\circ$  and standard pressure. Soluble in chloroform and in ether. Store in cylinders. It is usually packaged under pressure in liquid form.

**Incompatibility and stability.** Sulfite antioxidants can react with and inactivate sympathomimetics such as adrenaline.<sup>1</sup> Measures need to be taken to prevent such a reaction if sulfites have to be used. Cisplatin is another compound that can be inactivated.<sup>2</sup> Phenylmercuric nitrate may be inactivated or its activity enhanced.<sup>3,4</sup> Sulfites are reported to react with chloramphenicol.<sup>1</sup> Hydrogen peroxide generation has been reported on exposure to light of amino acid solutions containing sulfites.<sup>5</sup> When used in foods there can be a noticeable taste and a reduction in thiamine content.<sup>6</sup> Stability is affected by air and moisture,<sup>7</sup> and there is decomposition at very low pH.<sup>7</sup> There can be adsorption on to rubber closures.<sup>8</sup>

- Higuchi T, Schroeter LC. Reactivity of bisulfite with a number of pharmaceuticals. *J Am Pharm Assoc (Sci)* 1959; **48**: 535–40.
- Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharmaceutics* 1985; **24**: 91–9.
- Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; **24** (suppl): 84P–89P.
- Collins AJ, et al. Incompatibility of phenylmercuric acetate with sodium metabisulfite in eye drop formulations. *J Pharm Pharmacol* 1985; **37** (suppl): 123P.
- Brawley V, et al. Effect of sodium metabisulfite on hydrogen peroxide production in light-exposed pediatric parenteral amino acid solutions. *Am J Health-Syst Pharm* 1998; **55**: 1288–92.
- FAO/WHO. Evaluation of the toxicity of a number of antimicrobials and antioxidants: sixth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser* 228 1962.
- Stewart JT. Sodium metabisulfite. In: Rowe RC, et al. eds. *Handbook of pharmaceutical excipients*. 5th ed. London and Chicago: The Pharmaceutical Press, and the American Pharmaceutical Association 2006: 690–2.
- Schroeter LC. Sulfurous acid salts as pharmaceutical antioxidants. *J Pharm Sci* 1961; **50**: 891–901.

### Adverse Effects and Precautions

Gastric irritation due to liberation of sulfurous acid can follow ingestion of sodium metabisulfite and other sulfites. Large doses of sulfites may cause gastrointestinal upsets, respiratory or circulatory failure, and CNS disturbances.

Concentrated solutions of salts of sulfurous acid are irritant to skin and mucous membranes.

Sulfur dioxide is highly irritant to the eyes, skin, and mucous membranes. Inhalation results in irritation of the respiratory tract which may lead to bronchoconstriction and pulmonary oedema; very high concentrations may cause respiratory arrest and asphyxia. Contact with liquid sulfur dioxide results in acid burns. Allergic reactions including anaphylaxis and deaths have been reported.

The symbol † denotes a preparation no longer actively marketed

**Hypersensitivity.** Hypersensitivity reactions including bronchospasm, anaphylaxis, and some deaths have occurred in subjects, especially those with a history of asthma or atopic allergy, exposed to sulfites used as preservatives in foods.<sup>1</sup> These reactions have led to restrictions by the FDA on such use.<sup>2</sup> There have been case reports of reactions to sulfites in medicines;<sup>3,9</sup> such reports are considered to be few in number and the FDA has not extended the restriction on sulfites in foods to apply to their use in drugs since it was felt that in certain cases there was no suitable alternative to a sulfite.<sup>2</sup> It was even accepted that adrenaline recommended for use in treating allergic reactions could itself contain sulfite and that its presence should not preclude use of the adrenaline preparation even in sulfite-sensitive patients.<sup>2</sup>

- Anonymous. Sulfites in drugs and food. *Med Lett Drugs Ther* 1986; **28**: 74–5.
- Anonymous. Warning for prescription drugs containing sulfites. *FDA Drug Bull* 1987; **17**: 2–3.
- Baker GJ, et al. Bronchospasm induced by metabisulphite-containing foods and drugs. *Med J Aust* 1981; **ii**: 614–17.
- Twarog FJ, Leung DYM. Anaphylaxis to a component of isotheraline (sodium bisulfite). *JAMA* 1982; **248**: 2030–1.
- Koepke JW, et al. Dose-dependent bronchospasm from sulfites in isotheraline. *JAMA* 1984; **251**: 2982–3.
- Mikolich DJ, McCloskey WW. Suspected gentamicin allergy could be sulfite sensitivity. *Clin Pharm* 1988; **7**: 269.
- Deziel-Evans LM, Hussey WC. Possible sulfite sensitivity with gentamicin infusion. *DICP Ann Pharmacother* 1989; **23**: 1032–3.
- Campbell JR, et al. Allergic response to metabisulfite in lido-caine anesthetic solution. *Anesth Prog* 2001; **48**: 21–6.
- Riemersma WA, et al. Type IV hypersensitivity to sodium metabisulfite in local anaesthetic. *Contact Dermatitis* 2004; **51**: 148.

### Pharmacokinetics

Sulfites and metabisulfites are oxidised in the body to sulfate and excreted in the urine. Any sulfurous acid or sulfur dioxide is also converted to sulfate.

### Uses

Sulfur dioxide and the sulfites that produce sulfur dioxide and sulfurous acid are strong reducing agents and are used as antioxidants. Concentrations of the sulfites in pharmaceutical preparations have ranged from 0.01 to 1.0%. At higher concentrations and preferably at an acid pH sulfur dioxide and the sulfites exhibit antimicrobial activity.

Sulfur dioxide and the sulfites are used in the food industry as antioxidants, antimicrobial preservatives, and anti-browning agents. They are used in wine making where tableted sodium metabisulfite is commonly known as Campden Tablets. Concentrations of sulfites above 500 ppm impart a noticeable unpleasant taste to preparations. There is concern over the risk of severe allergic reactions arising from the use of sulfites in foods (see Hypersensitivity, above).

### Tar Acids

Alquitrán, ácidos de.

**Description.** Tar acids are phenolic substances derived from the distillation of coal tar or petroleum fractions. The lowest boiling fraction of coal tar, distilling at  $188^\circ$  to  $205^\circ$ , consists of mixed cresol isomers. The middle fraction, known as 'cresylic acids', distils at  $205^\circ$  to  $230^\circ$  and consists of cresols and xylenols. The 'high-boiling tar acids', distilling at  $230^\circ$  to  $290^\circ$ , consist mainly of alkyl homologues of phenol, with naphthalenes and other hydrocarbons. Cresol is described on p.1641.

- Black Fluids** are homogeneous solutions of coal-tar acids, or similar acids derived from petroleum, or any mixture of these, with or without hydrocarbons and with a suitable emulsifying agent.
- White Fluids** are finely dispersed emulsions of coal-tar acids, or similar acids derived from petroleum, or any mixture of these, with or without hydrocarbons.
- Modified Black Fluids and Modified White Fluids** may contain, as an addition, any other active ingredients, but if these are used, the type and amount must be disclosed, if required.

### Adverse Effects and Treatment

As for Phenol, p.1656.

Tar acids are generally very irritant and corrosive to the skin, even when diluted to concentrations used for disinfection.

**Poisoning.** A report of fatal self-poisoning in a 59-year-old man after the ingestion of about 250 mL of a xylene-containing disinfectant (*Stericol Hospital Disinfectant*).<sup>1</sup>

- Watson ID, et al. Fatal xylene self-poisoning. *Postgrad Med J* 1986; **62**: 411–12.

### Uses

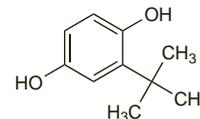
Tar acids are the phenolic components of coal tar and are used in the preparation of a range of fluids of varied activity used for household and general disinfection purposes.

Hydrocarbons are often used to enhance the activity of the tar acids in disinfectant fluids; they also help to reduce crystallisation of phenols.

### Tertiary Butylhydroquinone

Butilhidroquinona terciaria; TBHQ, 2-tert-butylhydroquinone.

$\text{C}_{10}\text{H}_{14}\text{O}_2 = 166.2$ .  
CAS — 1948-33-0.



### Profile

Tertiary butylhydroquinone is an antioxidant preservative used in foods. It has some antimicrobial activity.

### Tetrabromocresol

3,4,5,6-Tetrabromo-*o*-cresol.

$\text{C}_7\text{H}_4\text{Br}_4\text{O} = 423.7$ .  
CAS — 576-55-6.



### Profile

Tetrabromocresol is a brominated phenolic antiseptic. It has been used for hand disinfection and is applied topically in preparations for the treatment of fungal infections of the skin and bromhidrosis.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

**Multi-ingredient:** *Austral:* Pedoz; *Ger:* Gehwol Fungizid†.

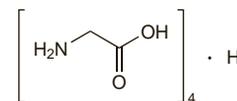
### Tetraglycine Hydroperiodide

Tetraglicina, hidroperioduro de.

Гидропериодид Тетраглицина

$\text{C}_{16}\text{H}_{42}\text{I}_7\text{N}_6\text{O}_{16} = 1490.9$ .

CAS — 7097-60-1.



### Profile

Tetraglycine hydroperiodide is an iodine-based disinfectant that is used in the emergency treatment of drinking water (p.1623).

### Preparations

**Proprietary Preparations** (details are given in Part 3)

**UK:** Potable Aqua; **USA:** Potable Aqua.

### Thiomersal (BAN, rINN)

Mercuriothiolate; Mercuriothiolate Sodique; Sodium Ethyl Mercuriothiosalicylate; Thimerosal; Thiomersalate; Thiomersalum; Thiomersaali; Thiomersal; Thiomersalis; Tiomerzál. Sodium (2-carboxyphenylthio)ethylmercury.

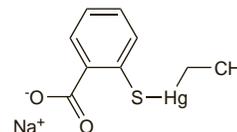
Тиомерсал

$\text{C}_9\text{H}_9\text{HgNaO}_2\text{S} = 404.8$ .

CAS — 54-64-8.

ATC — D08AK06.

ATC Vet — QD08AK06.



**Pharmacopoeias.** In *Eur.* (see p.vii) and *US*.

**Ph. Eur. 6.2** (Thiomersal). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble or soluble in alcohol; practically insoluble in dichloromethane. A 0.8% solution in water has a pH of 6.0 to 8.0. Protect from light.

**USP 31** (Thiomersal). A light cream-coloured crystalline powder with a slight characteristic odour. Soluble 1 in 1 of water and 1 in 12 of alcohol; practically insoluble in ether. A 1% solution in water has a pH of about 6.7. Store in airtight containers. Protect from light.

**Incompatibility.** Thiomersal is incompatible with acids, metal ions, and iodine. It forms precipitates with many alkaloids. The rate of oxidation of thiomersal in solution is greatly increased by traces of copper ions. In slightly acid solution thiomersal may be precipitated as the corresponding acid which undergoes slow decomposition with the formation of insoluble products. The activity of thiomersal may also be reduced by boric acid, edetic acid, or sodium thiosulfate or by the presence of blood or organic matter. Thiomersal may be adsorbed by plastic or rubber packaging materials.

References.

- Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; **24** (suppl): 84P–89P.
- Reader MJ. Influence of isotonic agents on the stability of thiomersal in ophthalmic formulations. *J Pharm Sci* 1984; **73**: 840–1.
- Morton DJ. EDTA reduces antimicrobial efficacy of thiomersal. *Int J Pharmaceutics* 1985; **23**: 357–8.

#### Adverse Effects, Treatment, and Precautions

As for Mercury, p.2341.

Hypersensitivity reactions occasionally occur. Allergic conjunctivitis has been reported.

◇ General references.

- Risher JF, et al. Organic mercury compounds: human exposure and its relevance to public health. *Toxicol Ind Health* 2002; **18**: 109–60.

**Hypersensitivity.** Both delayed (allergic contact) and immediate (including anaphylaxis and immune complex mediated disorders) hypersensitivity reactions have been associated with thiomersal.<sup>1</sup> The frequency of positive patch tests varies, with a Canadian centre reporting<sup>2</sup> an average incidence of 4.53% and a centre in the USA an incidence of 8.7%.<sup>3</sup> Most reactions are local and mild, involving application sites or blepharconjunctivitis from ocular preparations,<sup>1,4</sup> although there has been a report of acute laryngeal obstruction in a patient previously sensitised to the substance who used a throat spray preserved with thiomersal.<sup>5</sup> A case of occupational allergic contact dermatitis has been reported in a nurse as a result of contact with thiomersal as a preservative in childhood vaccines.<sup>6</sup> A generalised maculopapular eruption from an influenza vaccine containing thiomersal has also been reported.<sup>7</sup> The main source of sensitisation is thought to be thiomersal-preserved vaccines. Most people with patch tests positive to thiomersal are able to tolerate thiomersal-containing vaccines, although some individuals may experience reactions ranging from mild to serious.<sup>1</sup> If there is a definite history of anaphylaxis to thiomersal in any product, vaccines containing thiomersal should not be given. However, while anaphylaxis has not been shown to occur as a result of thiomersal in vaccines, it remains a theoretical risk.<sup>1</sup>

- National Advisory Committee on Immunization (NACI). Statement on thiomersal. *Can Commun Dis Rep* 2003; **29**: 1–10.
- Freiman A, et al. Patch testing with thiomersal in a Canadian centre: an 11-year experience. *Am J Contact Dermat* 2003; **14**: 138–43.
- Suneja T, Belsito DV. Thiomersal in the detection of clinically relevant allergic contact reactions. *J Am Acad Dermatol* 2001; **45**: 23–7.
- Wilson LA, et al. Delayed hypersensitivity to thiomersal in soft contact lens wearers. *Ophthalmology* 1981; **88**: 804–9.
- Maibach H. Acute laryngeal obstruction presumed secondary to thiomersal (merthiolate) delayed hypersensitivity. *Contact Dermatitis* 1975; **1**: 221–2.
- Kiec-Swierczynska M, et al. Occupational allergic contact dermatitis due to thiomersal. *Contact Dermatitis* 2003; **48**: 337–8.
- Lee-Wong M, et al. A generalized reaction to thiomersal from an influenza vaccine. *Ann Allergy Asthma Immunol* 2005; **94**: 90–4.

**Poisoning.** Serious adverse effects have followed parenteral and topical use of thiomersal.

Six poisonings (5 fatal) resulted from the use of 1000 times the normal concentration of thiomersal in a preparation of chloramphenicol for intramuscular injection.<sup>1</sup> There has also been a case report<sup>2</sup> of mercury poisoning associated with the intravenous use of high-dose hepatitis B immunoglobulin, preserved with thiomersal, after liver transplantation. Initial symptoms were paranoia, which rapidly progressed to severe dysarthria, static tremor, chorea, and decreased motor strength, as well as haemorrhagic gastritis. The patient responded well to chelation therapy.

Thiomersal used in topical antiseptic preparations was found to be toxic to epidermal cells.<sup>3</sup> After the death of 10 of 13 children as a result of treatment of omphaloceles (umbilical hernia) with a tincture of thiomersal, it was recommended that organic mercurial disinfectants be heavily restricted or withdrawn from hospital use as absorption occurred readily through intact membranes.<sup>4</sup>

A 44 year-old man who drank 83 mg/kg of a thiomersal-containing solution in an attempted suicide, spontaneously vomited after

15 minutes.<sup>5</sup> On admission to hospital a gastric lavage was performed and chelating drugs given. Despite this he developed gastritis, renal failure, dermatitis, gingivitis, delirium, polyneuropathy, respiratory failure, and coma. The patient was treated symptomatically, and 148 days after ingestion had recovered fully, except for sensory defects in two toes.

- Axton JHM. Six cases of poisoning after a parenteral organic mercurial compound (Merthiolate). *Postgrad Med J* 1972; **48**: 417–21.
- Lowell JA, et al. Mercury poisoning associated with high-dose hepatitis-B immune globulin administration after liver transplantation for chronic hepatitis B. *Liver Transpl Surg* 1996; **2**: 475–8.
- Anonymous. Topical antiseptics and antibiotics: organic mercurials. *Med Lett Drugs Ther* 1977; **19**: 83.
- Fagan DG, et al. Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic. *Arch Dis Child* 1977; **52**: 962–4.
- Pfah R, et al. Clinical course of severe poisoning with thiomersal. *J Toxicol Clin Toxicol* 1996; **34**: 453–60.

**Vaccines.** The use of thiomersal as a preservative in vaccines and its role as a possible cause of autism and neurodevelopmental disorders has been a controversial topic since 1999<sup>1</sup> when the regulatory authorities in both Europe<sup>2</sup> and the USA<sup>3</sup> issued statements recommending that the use of thiomersal in vaccines be phased out. This was based on the fact that the cumulative amount of mercury in the infant immunisation schedule potentially exceeds the recommended maximum level set by the US government for methyl mercury. More recently, however, a number of studies<sup>4</sup> have indicated a lack of association between thiomersal-containing vaccines and neurodevelopmental disorders such as autism and speech disorders. These findings were supported by the fact that thiomersal is metabolised to ethylmercury, which has substantially different pharmacokinetics to methylmercury. Ethylmercury is more rapidly excreted and does not accumulate in the body. The EMEA has issued a further statement<sup>5</sup> in which it confirmed that thiomersal could be used as a preservative when no alternative was available, subject to certain labelling requirements regarding hypersensitivity. The UK CSM<sup>6</sup> and the US FDA<sup>7</sup> have similarly concluded that there is no evidence of neurological adverse effects caused by the small amounts of thiomersal present in some vaccines; despite this, both endorse the view that the use of vaccines without thiomersal would be a prudent precautionary measure. WHO states<sup>8,9</sup> that there is no compelling scientific evidence of safety problems and advises that thiomersal-containing vaccines may continue to be used for global immunisation programmes because the benefit outweighs any theoretical risk of toxicity.

- Bigham M, Copes R. Thiomersal in vaccines: balancing the risk of adverse effects with the risk of vaccine-preventable disease. *Drug Safety* 2005; **28**: 89–101.
- European Agency for the Evaluation of Medicinal Products (EMA). EMEA public statement on thiomersal containing medicinal products (July 1999). EMEA publication no. 20962/99. Full version: <http://www.emea.europa.eu/pdfs/human/press/pus/2096299EN.pdf> (accessed 27/08/08)
- American Academy of Pediatrics, United States Public Health Service. Thiomersal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR* 1999; **48**: 563–5.
- Parker SK, et al. Thiomersal-containing vaccines and autistic spectrum disorder: a critical review of published original data. *Pediatrics* 2004; **114**: 793–804.
- European Agency for the Evaluation of Medicinal Products (EMA). EMEA public statement on thiomersal in vaccines for human use—recent evidence supports safety of thiomersal-containing vaccines (March 2004). EMEA publication no. 1194/04. Full version: <http://www.emea.europa.eu/pdfs/human/press/pus/119404en.pdf> (accessed 27/08/08)
- Committee on Safety of Medicines/Medicines and Healthcare Products Regulatory Agency. Safety of thiomersal-containing vaccines. *Current Problems* 2003; **29**: 9. Also available at: [http://www.mhra.gov.uk/home/idcplg?i=Service=GET\\_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased](http://www.mhra.gov.uk/home/idcplg?i=Service=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased) (accessed 16/03/06)
- FDA. Thiomersal in vaccines (updated June 2008). Available at: <http://www.fda.gov/cber/vaccine/thiomersal.htm> (accessed 11/08/08)
- WHO. Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines. *WHO Tech Rep Ser* 926 2004. Available at: [http://www.who.int/biologicals/publications/trs/areas/vaccines/thiomersal/Annex%204%20\(95-102\)TRS926thiomersal.pdf](http://www.who.int/biologicals/publications/trs/areas/vaccines/thiomersal/Annex%204%20(95-102)TRS926thiomersal.pdf) (accessed 16/03/06)
- WHO. Statement on thiomersal (issued July 2006). Available at: [http://www.who.int/vaccine\\_safety/topics/thiomersal/statement\\_jul2006/en/print](http://www.who.int/vaccine_safety/topics/thiomersal/statement_jul2006/en/print) (accessed 11/08/08)

#### Interactions

**Tetracyclines.** Nine patients using a contact lens solution containing 0.004% thiomersal developed varying degrees of ocular irritation after taking oral tetracyclines concurrently. Exposure to either the tetracyclines or thiomersal alone did not cause the response.<sup>1</sup>

- Crook TG, Freeman JJ. Reactions induced by the concurrent use of thiomersal and tetracycline. *Am J Optom Physiol Opt* 1983; **60**: 759–61.

#### Uses and Administration

Thiomersal is a bacteriostatic and fungistatic mercurial antiseptic that has been applied topically usually in a concentration of 0.1%. Its antibacterial action results from the release of ethylmercury after breakdown to thiosalicylate and ethylmercury.

Thiomersal, 0.001 to 0.01%, is used as a preservative in biological and pharmaceutical products. It has also been used to preserve solutions used in the care of contact lenses (p.1622).

#### Preparations

**USP 31:** Thiomersal Tincture; Thiomersal Topical Aerosol; Thiomersal Topical Solution.

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Lithorsan; Merthiolate; **Chile:** Intrasept; **Mon.:** Vitaseptol; **S.Afr.:** Merthiolate; Thiomersalate; **Thai:** Merthiolate; **USA:** Aeroaid; Mersol; **Venez.:** Merthiolate.

**Multi-ingredient:** **Spain:** Proskin; **Venez.:** Thimerfesa†.

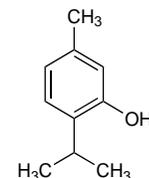
#### Thymol

Acido Timico; Isopropylmetacresol; Thymolum; Timol; Timolis; Tymol; Tymoli. 2-Isopropyl-5-methylphenol.

C<sub>10</sub>H<sub>14</sub>O = 150.2.

CAS — 89-83-8.

ATC Vet — QP53AX22.



**Pharmacopoeias.** In *Eur.* (see p.vii) and *Jpn.* Also in *USNF*.

**Ph. Eur. 6.2** (Thymol). Colourless crystals. The melting range is 48° to 52°. Very slightly soluble in water; very soluble in alcohol; freely soluble in volatile and in fixed oils; sparingly soluble in glycerol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

**USNF 26** (Thymol). Colourless, often large, crystals or a white crystalline powder with an aromatic thyme-like odour. The melting range is 48° to 51°; when melted it remains liquid at a considerably lower temperature. Soluble 1 in 1000 of water, 1 in 1 of alcohol and of chloroform, 1 in 1.5 of ether, and 1 in 2 of olive oil; soluble in glacial acetic acid and in fixed and volatile oils. Store in airtight containers. Protect from light.

**Incompatibility.** The antimicrobial activity of thymol is reduced by combination with protein.

#### Adverse Effects, Treatment, and Precautions

As for Phenol, p.1656.

When ingested, thymol is less toxic than phenol. It is irritant to the gastric mucosa. Fats and alcohol increase absorption and aggravate the toxic symptoms.

**Hypersensitivity.** Contact allergy to a heparinoid cream was due to an allergen formed by the reaction between thymol and the degradation products of a triazine derivative, both present as preservatives.<sup>1</sup>

- Smeenk G, et al. Contact allergy to a reaction product in Hirudoid cream; an example of compound allergy. *Br J Dermatol* 1987; **116**: 223–31.

#### Uses and Administration

Thymol is a phenolic antiseptic with antibacterial and antifungal activity. It is more powerful than phenol but its use is limited by its low solubility in water, irritancy, and susceptibility to protein.

Thymol is used chiefly as a deodorant in mouthwashes and gargles such as Compound Thymol Glycerin (BP 1988), an aqueous mixture of thymol 0.05% and glycerol 10% with colouring and flavouring, which may be used diluted with about 3 times its volume of warm water before use. Thymol has been used topically in the treatment of skin disorders and is also inhaled, with other volatile substances, for colds, coughs, and associated respiratory disorders.

Thymol 0.01% is added as an antioxidant to halothane, trichloroethylene, and tetrachloroethylene.

Thymol iodide is used in preparations for dental hygiene.

#### Preparations

**Proprietary Preparations** (details are given in Part 3)

**Ger.:** Medophyll†; **S.Afr.:** Cool Mint Listerine; Freshburst Listerine.

**Multi-ingredient:** **Arg.:** Fungicida†; Listerine Clasico; Listerine Cool Mint; Listerine Fresh Burst; Manzan; Novobronco†; Perioabacter Prof Avio; Vagicular; **Austral.:** SM-33; Vicks Vaporub; **Austria:** Alpicort; Crinon; DDD; Gingvan; Kinder Luuf; Luuf Balsam; Pe-Ce; Spasmo Claim; Thrombocid; Wick Vaporub; **Belg.:** Borostyrol; Dentopar; Perubore; Vicks Vaporub; **Braz.:** Anestiesio†; Angino-Rub; Cloraseptic; Cutisanol; Fluomint; Frixodon†; Gargotan†; Gyrol†; Lenidort†; Passaja†; Relampago†; Tabletes Valda†; Valda†; Wick Vaporub; **Canada.:** Antiseptic Mouthwash; Boil Ease†; Buckley's White Rub†; Carboseptol†; Lipsorex Plus; Lipsorex†; Listerine; Listerine Antiseptic Tartar Control; Mouthwash Antiseptic & Gargle†; Nasal Jelly†; Thermo-Gel; Valda; Vaporisateur Medicament; Vaporizing Ointment; **Chile:** Balsamo Leon†; Galutecl†; Hansaplast Descongestionante; Listerine; Listermint Con Fluor; Oralfresh Citrus; Oralfresh Citrus; Polisept†; **Cz.:** Parodontal F5†; Pinosol; Septolete†; **Fin.:** Vicks Vaporub; **Fr.:** Borostyrol; Listerine; Listerine protection dents et gencives; Moustidose; Nisacalm; Pastilles Medicinales Vicks; Perubore; Valda; Vicks Vaporub; **Ger.:** Alfem†; Crinon†; Em-medical†; Nasentropfen-ratiopharm†; Oestrogol N†; Pulmoton†; Retterszip Ausserlich†; Retterszip Quick; Saliathymol N†; Thrombocid; **Gr.:** Oulogram; **Hong Kong:** Burn Cream†; Cool Mint Listerine; Gly Thymol; Kamistad; Listerine; Listerine Tartar Control; Listerine Teeth and