

Lanterbine; Terbron; Terbuta; Tolbin; Vida-Butaline; **Hung.**: Bricanyl; **India**: Bricanyl; **Indon.**: Astherin; Brasmatic; Bricsma; Forasma; Lasmalin; Nairer; Pulmobron; Relivan; Sedakten; Tabas; Terasma; Tismalin; Yarisma; **Irl.**: Bricanyl; **Israel**: Bricalin; Terbulin; **Ital.**: Bricanyl; **Malaysia**: Ataline; Bricanyl; Bucanil; Butaline; Butanil; Terbron; Terbulin; Tolbin; Bricanyl; Tazikent; Terbuken; **Neth.**: Bricanyl; Terbasmin; **Norw.**: Bricanyl; **NZ**: Bricanyl; **Philipp.**: Alloxgen; Astebrom; Bricanyl; Bronchodami; Pulmonary; Pulmoxel; Terbulin; **Port.**: Bricanyl; **S.Afr.**: Bricanyl; **Singapore**: Ataline; Bricanyl; Bucanil; Tolbin; **Spain**: Tedipulmo; Terbasmin; **Swed.**: Bricanyl; **Switz.**: Bricanyl; **Thai**: Asmaline; Asthmasian; Bricanyl; Broncholine; Bronchonyl; Bronco Asmo; Bucanil; Cencanyl; Med-Broncodil; Proasma-T; Sulterline; Terbron; Terbulino; Tolbin; Vacanyl; **Turk.**: Bricanyl; **UK**: Bricanyl; Monovent; **USA**: Brethine; Bricanyl; **Venez.**: Bricanil; Nortol.

**Multi-ingredient:** **Austria**: Bricanyl comp; **Braz.**: Bricanyl Composto; **Ger.**: Bricanyl comp; **Hong Kong**: Bricanyl Expectoant; **India**: Asconil +; Asmotone Plus; Bricarex; Bro-Zedex; Bronchosolvin; Cof QX; Gnilinctus-BM; Mucaryl-AX; Mucosol; Okaril Plus; Tergil; Tergil-T; Terpect; Terphylate; Terphylin; Theobric; Toscof; Tuspel Plus; **Indon.**: Bricsma Expectoant; Terasma Expectoant; **Irl.**: Bricanyl Expectoant; **Mex.**: Bricanyl EX; **Philipp.**: Bricanyl Expectoant; **S.Afr.**: Berylin Bronchospect; Bronchoped; Bronchospect; **Spain**: Terbasmin Expectoante; **Thai**: Bricanyl Expectoant; Colbron; Med-Broncodil Expectoant; Terbosil; Terbron Expectoant; Tolbin.

## Theobromine (BAN)

Santheose; Teobromini; Teobromin; Teobromina; Teobrominas; Theobromin; Théobromine; Theobrominum. 3,7-Dihydro-3,7-dimethylpurine-2,6(1H)-dione; 3,7-Dimethylxanthine.

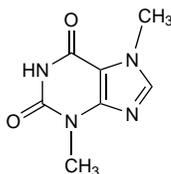
Теобромин

$C_7H_8N_4O_2 = 180.2$ .

CAS — 83-67-0.

ATC — C03BD01; R03DA07.

ATC Vet — QC03BD01; QR03DA07.



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

**Ph. Eur. 6.2** (Theobromine). A white or almost white powder. Very slightly soluble in water and in dehydrated alcohol; slightly soluble in ammonia. It dissolves in dilute solutions of alkali hydroxides and in mineral acids.

### Profile

Theobromine has the general properties of the other xanthines (see Theophylline, p.1140). It has a weaker activity than theophylline or caffeine and has practically no stimulant effect on the CNS. Large doses can cause nausea and vomiting. Theobromine has been used for its bronchodilating properties and in the treatment of cardiovascular disorders. Theobromine and calcium salicylate (theosalicin), theobromine and sodium acetate, and theobromine and sodium salicylate (themisalium, theobromsal) have all been used similarly to theobromine.

Theobromine is the chief xanthine in the beverage cocoa (p.2415). It is also present in chocolate and in small amounts in tea. Theobroma oil may contain up to 2% theobromine.

### Preparations

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

**Multi-ingredient:** **Austria**: Asthma-Hilfe; **Braz.**: Urodonalf.

## Theophylline (BAN)

Anhydrous Theophylline; Teofilin; Teofilina; Teofilinas; Teofilin; Teofilina; Teofilini; Teofilin; Theofyllin; Théophylline; Theophyllinum. 3,7-Dihydro-1,3-dimethylpurine-2,6(1H)-dione; 1,3-Dimethylxanthine.

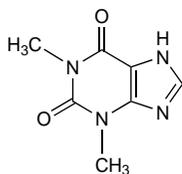
Теофиллин

$C_7H_8N_4O_2 = 180.2$ .

CAS — 58-55-9.

ATC — R03DA04.

ATC Vet — QR03DA04.



**Pharmacopoeias.** In *Eur.* (see p.vii), *Jpn*, *US*, and *Viet*. Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

**Ph. Eur. 6.2** (Theophylline). A white or almost white, crystalline

powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

**USP 31** (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

### Theophylline Hydrate (BANM)

Teofilina monohidrat; Teofilinas monohidratas; Teofilinimono-hydrataati; Teofilinimono-hydrat; Theofyllin monohydrát; Theophylline Monohydrate; Théophylline monohydraté; Theophyllinum monohydricum.

Теофиллин Гидрат

$C_7H_8N_4O_2 \cdot H_2O = 198.2$ .

CAS — 5967-84-0.

ATC — R03DA04.

ATC Vet — QR03DA04.

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *US*, and *Viet*. Some pharmacopoeias include anhydrous and hydrated theophylline in one monograph.

**Ph. Eur. 6.2** (Theophylline Monohydrate; Theophylline Hydrate BP 2008). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol. It dissolves in solutions of alkali hydroxides, in ammonia, and in mineral acids.

**USP 31** (Theophylline). It contains one molecule of water of hydration or is anhydrous. It is a white, odourless, crystalline powder. Slightly soluble in water, more soluble in hot water; sparingly soluble in alcohol, in chloroform, and in ether; freely soluble in solutions of alkali hydroxides and in ammonia.

**Stability.** Alcohol-free theophylline liquid repackaged in clear or amber polypropylene oral syringes could be stored at room temperature under continuous fluorescent lighting for at least 180 days without significant change in the concentration of theophylline.<sup>1</sup> However, it was recommended that solutions be protected from light because of the potential for discoloration.

Extemporaneous oral preparations of theophylline 5 mg/mL in commercial suspension vehicles were found<sup>2</sup> to be stable for up to 90 days in amber plastic bottles stored at 23° to 25°.

1. Johnson CE, Drabik BT. Stability of alcohol-free theophylline liquid repackaged in plastic oral syringes. *Am J Hosp Pharm* 1989; **46**: 980-1.
2. Johnson CE, et al. Stability of anhydrous theophylline in extemporaneously prepared alcohol-free oral suspensions. *Am J Health-Syst Pharm* 2005; **62**: 2518-20.

### Adverse Effects

The adverse effects commonly encountered with theophylline and xanthine derivatives irrespective of the route, are gastrointestinal irritation and stimulation of the CNS. Serum concentrations of theophylline greater than 20 micrograms/mL (110 micromol/litre) are associated with an increased risk of adverse effects (but see below).

Theophylline may cause nausea, vomiting, abdominal pain, diarrhoea, and other gastrointestinal disturbances, insomnia, headache, anxiety, irritability, restlessness, tremor, and palpitations. Overdosage may also lead to agitation, diuresis and repeated vomiting (sometimes haematemesis) and consequent dehydration, cardiac arrhythmias including tachycardia, hypotension, electrolyte disturbances including profound hypokalaemia, hyperglycaemia, hypomagnesaemia, metabolic acidosis, rhabdomyolysis, convulsions, and death. Severe toxicity may not be preceded by milder symptoms. Convulsions, cardiac arrhythmias, severe hypotension, or cardiac arrest may follow rapid intravenous injection, and fatalities have been reported. The drug is too irritant for intramuscular use. Proctitis may follow repeated use of suppositories.

◊ Adverse effects are uncommon at serum-theophylline concentrations of 5 to 10 micrograms/mL but become more frequent at 15 micrograms/mL or above, and are greatly increased in frequency and severity at concentrations greater than 20 micrograms/mL.<sup>1-3</sup> The severity of toxicity is generally correlated with age, underlying disease, and serum-theophylline concentration, but a distinction has been made between acute and chronic theophylline intoxication; symptoms appear to occur at a lower theophylline concentration in chronic toxicity than after acute ingestion of large amounts.<sup>1,2,4,5</sup> Young infants and the elderly (over 60 years) appear to be at particular risk from chronic intoxication with theophylline.<sup>6,7</sup> Older patients with chronic intoxication may be at greater risk of major toxic effects, such as arrhythmias, seizures, and death, than those with acute intoxication.<sup>5</sup>

Common clinical manifestations of theophylline toxicity after overdosage of aminophylline or theophylline include nausea, vomiting, diarrhoea, agitation, tremor, hypertonicity, hyperventilation, supraventricular and ventricular arrhythmias, hypotension, and seizures. Metabolic disturbances such as hypokalaemia, hyperglycaemia, hypophosphataemia, hypercalcaemia, metabolic acidosis, and respiratory alkalosis often occur.<sup>1-3</sup> Other toxic effects reported include dementia,<sup>8</sup> toxic psychosis,<sup>9</sup> symptoms of acute pancreatitis,<sup>10</sup> rhabdomyolysis<sup>11-13</sup> with associated renal failure,<sup>11</sup> and acute compartment syndrome.<sup>14</sup>

Serious toxic symptoms may not be preceded by minor symptoms. In acute intoxication with sustained-release preparations the onset of major toxic symptoms may be delayed for up to 24 hours<sup>1</sup> and prolonged monitoring of such patients is required. Patients have recovered despite serum-theophylline concentrations in excess of 200 micrograms/mL<sup>12,14</sup> but fatalities have occurred with much lower serum concentrations.<sup>10,15,16</sup> Mortality in severe poisoning may be as high as 10%.

1. Dawson AH, Whyte IM. The assessment and treatment of theophylline poisoning. *Med J Aust* 1989; **151**: 689-93.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15**: 471-81.
3. Hardy CC, Smith J. Adverse reactions profile: theophylline and aminophylline. *Prescribers' J* 1997; **37**: 96-101.
4. Olson KR, et al. Theophylline overdose: acute single ingestion versus chronic repeated overmedication. *Am J Emerg Med* 1985; **3**: 386-94.
5. Shannon M. Life-threatening events after theophylline overdose: a 10-year prospective analysis. *Arch Intern Med* 1999; **159**: 989-94.
6. Shannon M, Lovejoy FH. Effect of acute versus chronic intoxication on clinical features of theophylline poisoning in children. *J Pediatr* 1992; **121**: 125-30.
7. Shannon M. Predictors of major toxicity after theophylline overdose. *Ann Intern Med* 1993; **119**: 1161-7.
8. Drummond I. Aminophylline toxicity in the elderly. *BMJ* 1982; **285**: 779-80.
9. Wasser WG, et al. Theophylline madness. *Ann Intern Med* 1981; **95**: 191.
10. Burgan THS, et al. Fatal overdose of theophylline simulating acute pancreatitis. *BMJ* 1982; **284**: 939-40.
11. Macdonald JB, et al. Rhabdomyolysis and acute renal failure after theophylline overdose. *Lancet* 1985; **i**: 932-3.
12. Rumpf KW, et al. Rhabdomyolysis after theophylline overdose. *Lancet* 1985; **i**: 1451-2.
13. Modi KB, et al. Theophylline poisoning and rhabdomyolysis. *Lancet* 1985; **ii**: 160-1.
14. Lloyd DM, et al. Acute compartment syndrome secondary to theophylline overdose. *Lancet* 1990; **ii**: 312.
15. Whyte KF, Addis GJ. Toxicity of salbutamol and theophylline together. *Lancet* 1983; **ii**: 618-19.
16. Davies RJ, Hawkey CJ. Fatal theophylline toxicity precipitated by in situ pulmonary artery thrombosis. *Postgrad Med J* 1989; **65**: 49-50.

**Effects on carbohydrate metabolism.** Hyperglycaemia is frequent in theophylline intoxication, and is thought to be secondary to theophylline-induced adrenal catecholamine release.<sup>1,2</sup> Whether the effects on blood glucose are significant at more modest serum concentrations of theophylline is unclear, although in 29 preterm infants, mean plasma-glucose concentrations were significantly higher after treatment with intravenous aminophylline and oral theophylline than in those not treated. Two of 15 treated infants developed clinically significant hyperglycaemia and glycosuria. It was recommended that plasma-glucose concentrations be monitored in preterm infants receiving theophylline.<sup>3</sup>

1. Kearney TE, et al. Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; **102**: 766-9.
2. Shannon M. Hypokalaemia, hyperglycaemia and plasma catecholamine activity after severe theophylline intoxication. *J Toxicol Clin Toxicol* 1994; **32**: 41-7.
3. Srinivasan G, et al. Plasma glucose changes in preterm infants during oral theophylline therapy. *J Pediatr* 1983; **103**: 473-6.

**Effects on electrolytes.** Hypokalaemia is a common metabolic disturbance in theophylline intoxication, but it has also been reported<sup>1</sup> in patients with plasma-theophylline concentrations within the therapeutic range. It is considered to be secondary to theophylline-induced adrenal catecholamine release, with cellular influx of potassium ions.<sup>2</sup> It is recommended<sup>1</sup> that plasma-potassium is monitored during intravenous theophylline therapy particularly if other drugs predisposing to hypokalaemia are also given (see also Interactions, below). Hypophosphataemia<sup>1,3</sup> and hyponatraemia<sup>1</sup> can also occur at therapeutic plasma-theophylline concentrations. Hypomagnesaemia<sup>4</sup> and hypercalcaemia<sup>5</sup> have occurred in theophylline overdose.

1. Zantvoort FA, et al. Theophylline and serum electrolytes. *Ann Intern Med* 1986; **104**: 134-5.
2. Minton NA, Henry JA. Acute and chronic human toxicity of theophylline. *Hum Exp Toxicol* 1996; **15**: 471-81.
3. Laaban J-P, et al. Hypophosphatemia complicating management of acute severe asthma. *Ann Intern Med* 1990; **112**: 68-9.
4. Hall KW, et al. Metabolic abnormalities associated with intentional theophylline overdose. *Ann Intern Med* 1984; **101**: 457-62.
5. McPherson ML, et al. Theophylline-induced hypercalcaemia. *Ann Intern Med* 1986; **105**: 52-4.

**Effects on the heart.** **ARRHYTHMIAS.** Theophylline or aminophylline can precipitate sinus tachycardia and supraventricular and ventricular premature contractions at therapeutic serum-theophylline concentrations<sup>1</sup> and in overdose.<sup>2,3</sup> Multifocal atrial tachycardia has also been associated with both theophylline overdose<sup>2</sup> and serum-theophylline concentrations within the generally accepted therapeutic range of 10