Food allergy. Oral sodium cromoglicate has been used in the prophylaxis of food allergy reactions (p.564). However, efficacy has not been unequivocally established.

Mastocytosis. Mastocytosis is a rare condition characterised by abnormal proliferation of mast cells and their accumulation in body tissues.[1-3] Signs and symptoms of the disease result from the spontaneous or induced release of mast cell mediators. Mastocytosis occurs in cutaneous or systemic forms, which are further subdivided based on clinical presentation and prognosis. Clinical algorithms and recommendations for diagnosis, treatment, and response criteria have been developed.[4]

- *Cutaneous mastocytosis* most often manifests as urticaria pigmentosa (disseminated red-brown macules, papules, or plaques); other symptoms include flushing, pruritus, urticaria, blistering, and dermatographism. Mastocytomas may occur as brownish solitary or multiple nodular accumulations of mast cells. In children with cutaneous mastocytosis, symptoms will resolve in about half by adolescence.
- *Systemic mastocytosis* can involve diverse organs and tissues including the bones, liver, spleen, lymph nodes, haematopoietic system, gastrointestinal tract, and also the skin. General symptoms include fatigue, weight loss, fever, and sweats. Gastrointestinal complaints such as abdominal pain and diarrhoea are common, and some patients may experience malabsorption, steatorrhoea, or peptic ulcer disease. Bone marrow involvement may result in bone pain, osteoporosis, fractures, bone marrow fibrosis, and myeloproliferative and myelodysplastic diseases. Other systemic effects include lymphadenopathy, hepatosplenomegaly, headache and other neuropsychiatric symptoms, syncope, and anaphylactoid reactions.

Avoidance of trigger factors is an important measure in the management of mastocytosis. Such factors include exposure to extremes of cold or heat (hot bath or sunbathing), emotional stress, mechanical irritation (vigorous towel rubbing, massage), infections, alcohol, some drugs (e.g. aspirin, NSAIDs, opioid analgesics, sympathomimetics, polymyxin B, dextran, radiographic dyes), and animal venoms.[1,2,5]

Treatment is aimed at relieving symptoms and does not alter the course of the disease.[1,2,4-6] H_1-antagonist antihistamines such as hydroxyzine and cyproheptadine are used to provide relief of flushing, pruritus, urticaria, blistering, and abdominal pain. Patients at risk of anaphylactoid reactions should carry adrenaline for self-injection, and those who have repeated reactions should be given prophylactic antihistamines. H_2-antagonist antihistamines such as cimetidine, and proton pump inhibitors such as omeprazole, are used to manage gastrointestinal symptoms, particularly gastritis and peptic ulcer disease. Bisphosphonates may be helpful for osteopenia and bone pain. Sodium cromoglicate is given to manage abdominal pain, nausea, and diarrhoea. It may also provide some relief of headache, neuropsychiatric symptoms, and skin symptoms in some patients. Photochemotherapy using an oral psoralen with ultraviolet A irradiation (PUVA—see p.1606) has been used to reduce cutaneous manifestations of mastocytosis, but urticaria pigmentosa usually recurs within several weeks. Topical PUVA appears to be ineffective. Mastocytomas that cause symptoms may be treated with local PUVA or potent topical corticosteroids. Although surgical removal may be considered, the majority of mastocytomas will involute spontaneously.

Other treatments have also been tried in the treatment of small numbers of patients with aggressive systemic mastocytosis. Mixed results have been reported with the use of interferon alfa.[1] There is a report of ciclosporin with methylprednisolone being used successfully.[4] Imatinib has been used successfully in systemic mastocytosis with associated eosinophilia and with a mutation of the platelet-derived growth factor receptor-α gene on chromosome 4q12.[6] Beneficial responses to cladribine have also occurred in a small number of patients with systemic disease.[6,7]

1. Hartmann K, Henz BM. Mastocytosis: recent advances in defining the disease. *Br J Dermatol* 2001; **144:** 682–95.
2. Carter MC, Metcalfe DD. Paediatric mastocytosis. *Arch Dis Child* 2002; **86:** 315–19.
3. Castells MC. Mastocytosis: classification, diagnosis, and clinical presentation. *Allergy Asthma Proc* 2004; **25:** 33–6.
4. Valent P, *et al.* Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007; **37:** 435–53.
5. Almahroos M, Kurban AK. Management of mastocytosis. *Clin Dermatol* 2003; **21:** 274–7.
6. Tefferi A, Pardanani A. Systemic mastocytosis: current concepts and treatment advances. *Curr Hematol Rep* 2004; **3:** 197–202.
7. Kluin-Nelemans HC, *et al.* Cladribine therapy for systemic mastocytosis. *Blood* 2003; **102:** 4270–6.

Rhinitis and conjunctivitis. Many drugs, including sodium cromoglicate, are used in the management of allergic rhinitis (p.565) and conjunctivitis (p.564). There is some evidence that nedocromil[1] or lodoxamide[2] may be more effective than cromoglicate in the management of vernal keratoconjunctivitis.

1. El Hennawi M. A double-blind placebo controlled group comparative study of ophthalmic sodium cromoglycate and nedocromil sodium in the treatment of vernal keratoconjunctivitis. *Br J Ophthalmol* 1994; **78:** 365–9.
2. Leonardi A, *et al.* Effect of lodoxamide and disodium cromoglycate on tear eosinophil cationic protein in vernal keratoconjunctivitis. *Br J Ophthalmol* 1997; **81:** 23–6.

Preparations

BP 2008: Sodium Cromoglicate Eye Drops; Sodium Cromoglicate Powder for Inhalation;
USP 31: Cromolyn Sodium Inhalation Powder; Cromolyn Sodium Inhalation Solution; Cromolyn Sodium Nasal Solution; Cromolyn Sodium Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Claroftal; Clo-5†; Intal; Klonalcrom; Sificrom†; ***Austral.:*** Cromese; Intal; Opticrom; Rynacrom; ***Austria:*** Acromax; Aeropaxyn†; Allergo-COMOD; Coldacrom; Cromal†; Cromoglin; Cromophtal; Intal; Lomusol; Vividrin; ***Belg.:*** Cromabak; Cromonez-Pos; Cromophta-Pos; Lomudal; Lomusol; Opticrom; ***Braz.:*** Cromabak; Cromocato; Cromolerg; Intal; Maxicrom; Rilan†; ***Canad.:*** Apo-Cromolyn; Cromolyn; Gen-Cromolyn†; Intal; Nalcrom; Opticrom; Solu-Crom; ***Chile:*** Oftacon; ***Cz.:*** Allergo-COMOD; Allergocrom; Cromobene; Cromogen†; Cromohexal; Cromolyn†; Cusicrom; DNCG†; Hay-Crom†; Intal†; Lecrolyn; Nalcrom; Stadaglicin†; Steri-Neb Cromogen†; Vividrin†; ***Denm.:*** Hexacromant†; Lecrolyn; Lomudal; ***Fin.:*** Glinor; Lecrolyn; Lomudal; ***Fr.:*** Allergo-COMOD†; Alloptrex; Cromabak; Cromadoses; Cromoptic; Cromosoft†; Intercron; Lomudal; Lomusol; Multicrom; Nalcron†; Ophtacalm; Opticron; ***Ger.:*** Acecromol†; Alerg†; Allergo-COMOD; Allergocrom; Allergoval; Colimune; Crom-Ophtal; Cromo; Cromoglicin†; Cromohexal; Cromolind; Cromopp; Diffusyl; Dispacromil; DNCG; duracromant†; Fenistil†; Flenid†; Flui-DNCG; Intal; IsoCrom; Lomupren; Opticrom; Otriven H†; Padiacrom; Pentacrom†; Pentatop; Pulbil†; Siozwo Allerg†; Vividrin; ***Gr.:*** Allergojovis; Allergostop; Allergotin; Botastin; Crolidin†; Cromabak; Cromo-POS; Cromodal; Cromolergin UD; Duobetic†; Erystamine-K; Fluvet†; Indoprex†; Iopanchol; Kaosyl; Lomudal; Nalcrom; Spaziron; Ufocollyre; Vekfanol; Vividrin; Zineli; Zulboral; ***Hong Kong:*** Cromabak; Cromal; Intal†; Mitayaku; Opticrom†; Stadaglicin; ***Hung.:*** Cromohexal; Cromolyn†; Cusicrom†; Intal; Lecrolyn; Opticrom; Stadaglicin†; Taleum; ***India:*** Cromal; Fintal†; ***Indon.:*** Crom-Ophtal; ***Irl.:*** Cromogen; Hay-Crom; Intal; Nalcrom; Opticrom; Rynacrom; Vividrin; ***Israel:*** Cromogen†; Cromolyn; Cromoptic; Cronase; Lomudal; Opticrom; Vicrom; ***Ital.:*** Acticrom†; Brunicrom; Cromabak; Cromantal; Cromosan†; Frenal†; Gastrofrenal; Lomudal; Lomuspray†; Nalcrom; Sificrom; ***Jpn:*** Intal; ***Malaysia:*** Allergocrom†; Cusicrom; Intal†; Opticrom; Stadaglicin; Vividrin†; ***Mex.:*** Alercrom; Exaler†; Intal; Livari; Maxicrom; Oftacon†; Opticrom; Rynacrom; Spralyn; ***Mon.:*** Zallyre; ***Neth.:*** Allerg-Abak; Allergo-COMOD; Allergocrom†; Lomudal; Lomusol; Nalcrom; Opticrom; Otrivin hooikoorts†; Prevalin; Vividrin; ***Norw.:*** Lecrolyn; Lomudal; ***NZ:*** Cromolux; Intal; Nalcrom; Opticrom; Optrex Hayfever Allergy; Rynacrom; Vicrom; ***Philipp.:*** Cromabak; Lecrolyn; Vividrin; ***Pol.:*** Allergo-COMOD; Allergocrom; Cromogen; Cromohexal; Cromosol; Cromoxal; Cropoz G; Cusicrom; Lecrolyn; Nalcrom; Polcrom; Vividrin; ***Port.:*** Croglina; Cromabak; Cromex†; Cusicrom†; Davicrome; Fenolip; Intal; Opticrom; Rynacrom†; ***Rus.:*** Cromoglin (Кромоглин); Cromohexal (Кромогексал); Cropoz (Кропоз); Hay-Crom (Хай-кром); Ifiral (Ифирал); Intal (Интал); Lecrolyn (Лекролин); ***S.Afr.:*** Cromabak†; Cromohexal; Stop-Allerg; Vividrin†; ***Singapore:*** Cromabak; Intal; Opticrom; Rynacrom†; Sificrom†; Vividrin; ***Spain:*** Alergocrom; Cromo Asma†; Cusicrom; Farmacrom; Frenal; Gastrofrenal; Intal†; Nebulasma; Nebulcrom; Poledin†; Primover; Renocil; Rinilyn†; Rinofrenal; ***Swed.:*** Lecrolyn; Lomudal; Pollyferm; Rinil†; ***Switz.:*** Allergo-COMOD; Cromabak; Cromodyn; Cromosol ophta; Cromosol UD; Glicinal†; Lomudal; Lomusol; Nalcrom; Opticrom; Vividrin; ***Thai.:*** Intal; Lecrolyn†; Opticrom†; Rynacrom; Vividrin; ***Turk.:*** Allergo-COMOD; Allergocrom; Allersol; Intal; Opticrom; Rynacrom; ***UK:*** Clariteyes; Clarityn; Cromogen†; Hay-Crom; Hayfever Eye Drops; Intal; Nalcrom; Opticrom; Optrex Allergy; Pollenase Allergy; Rynacrom; Vivicrom; Vividrin; ***USA:*** Crolom; Gastrocrom; Intal; Nasalcrom; Opticrom; ***Venez.:*** Alergocrom†; Cromisol; Cromo-Spray†; Cromoftal; Maxicrom†.

Multi-ingredient: ***Arg.:*** Duotec†; Hyalcrom; Rinogel; ***Austria:*** Ditec; ***Cz.:*** Allergocrom Kombi; Ditec†; Intal Plus†; ***Ger.:*** Aarane N; Allergospasmin; Ditec†; Lomupren compositum†; ***Hung.:*** Duotec†; ***India:*** Asthacrom; ***Ital.:*** Cromozil; Rinofrenal; Visuglican; ***Malaysia:*** Rynacrom Compound†; ***Port.:*** Rinoglin†; ***Rus.:*** Ditec (Дитек); ***Spain:*** Frenal Compositum; Rinofrenal Plus; ***Switz.:*** Aarane†; Allergospasmine†; Lomusol-X†; ***Thai.:*** Rynacrom Compound†; ***Turk.:*** Rynacrom Compound; ***UK:*** Rynacrom Compound†.

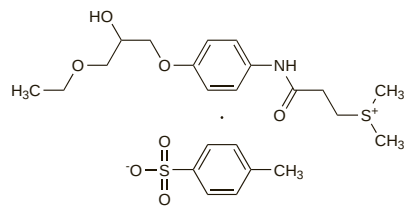
Suplatast Tosilate *(rINN)*

IPD-1151T; Suplatast, Tosilate de; Suplatast Tosylate; Suplatastum Tosilas; Tosilato de suplatast. (±)-(2-{[*p*-(3-Ethoxy-2-hydroxypropoxy)phenyl]carbamoyl}ethyl)dimethylsulphonium *p*-toluenesulphonate; (3-{[4-(3-Ethoxy-2-hydroxypropoxy)phenyl]amino}-3-oxopropyl)dimethylsulphonium *p*-toluenesulphonate.

Супластаст Тозилат

$C_{23}H_{33}NO_7S_2$ = 499.6.

CAS — 94055-76-2.



Profile

Suplatast tosilate is an anti-allergic given orally in the prophylactic management of asthma and other allergic conditions.

◊ References.

1. Sano Y, *et al.* Anti-inflammatory effect of suplatast tosilate on mild asthma. *Chest* 1997; **112:** 862–3.
2. Nihei Y, *et al.* Suplatast tosilate (IPD), a new immunoregulator, is effective in vitiligo treatment. *J Dermatol* 1998; **25:** 250–5.
3. Tamaoki J, *et al.* Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependent asthma: a double-blind randomised study. *Lancet* 2000; **356:** 273–8.
4. Shioya T, *et al.* Effect of suplatast tosilate, a Th2 cytokine inhibitor, on cough variant asthma. *Eur J Clin Pharmacol* 2002; **58:** 171–6.
5. Matsuda Y, *et al.* Improvement of alanine aminotransferase by administration of suplatast tosilate plus ursodeoxycholic acid in patients with resistance to ursodeoxycholic acid monotherapy on hepatitis C virus-related chronic liver disease. *Intern Med* 2002; **41:** 774–9.
6. Sakuma-Oyama Y, *et al.* A case of recurrent cutaneous eosinophilic vasculitis: successful adjuvant therapy with suplatast tosilate. *Br J Dermatol* 2003; **149:** 901–3.
7. Sano T, *et al.* Higashishikoku Asthma Research Group. Add-on effects of suplatast tosilate in bronchial asthma patients treated with inhaled corticosteroids. *Lung* 2003; **181:** 227–35.
8. Teraki Y, Fukuda T. Pemphigoid nodularis associated with psoriatic erythroderma: successful treatment with suplatast tosilate. *Br J Dermatol* 2008; **158:** 424–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: IPD.

Terbutaline Sulfate *(USAN, rINNM)* ⊗

KWD-2019; Sulfato de terbutalina; Terbutaliinisulfaatti; Terbutalin Sülfat; Terbutaline, sulfate de; Terbutaline Sulphate *(BANM)*; Terbutalini sulfas; Terbutalino sulfatas; Terbutalinsulfat; Terbutalinsulfát; Terbutalin-szulfát. 2-*tert*-Butylamino-1-(3,5-dihydroxyphenyl)ethanol sulphate.

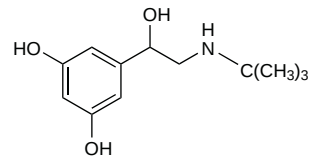
Тербуталина Сульфат

$(C_{12}H_{19}NO_3)_2,H_2SO_4$ = 548.6.

CAS — 23031-25-6 (terbutaline); 23031-32-5 (terbutaline sulfate).

ATC — R03AC03; R03CC03.

ATC Vet — QR03AC03; QR03CC03.



(terbutaline)

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

Ph. Eur. 6.2 (Terbutaline Sulphate). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol.

USP 31 (Terbutaline Sulfate). A white to grey-white crystalline powder; odourless or has a faint odour of acetic acid. Soluble in water and in 0.1N hydrochloric acid; insoluble in chloroform; slightly soluble in methyl alcohol. Store at 15° to 30°. Protect from light.

Adverse Effects and Precautions

As for Salbutamol, p.1131.

Overdosage. An overdose of terbutaline due to transcutaneous absorption has been reported after inappropriate topical application to skin infected with tinea.[1] Transcutaneous absorption should be considered especially when children with facial eczema or dermatitis are given terbutaline via a nebuliser and mask.

For general effects of $beta_2$ agonists after overdose, see Salbutamol p.1132.

1. Ingrams GJ, Morgan FB. Transcutaneous overdose of terbutaline. *BMJ* 1993; **307:** 484.

Pulmonary oedema. Pulmonary oedema has occurred in women given $beta_2$ agonists, including terbutaline, for premature labour.[1] The risk factors, the most important of which is fluid overload, are discussed under Precautions for Salbutamol, p.1132.

1. Perry KG, *et al.* Incidence of adverse cardiopulmonary effects with low-dose continuous terbutaline infusion. *Am J Obstet Gynecol* 1995; **173:** 1273–7.

Tolerance. As with other $beta_2$ agonists (see p.1132) there is some evidence[1] that tolerance may develop to terbutaline when it is used regularly.

1. Hancox RJ, *et al.* Tolerance to beta-agonists during acute bronchoconstriction. *Eur Respir J* 1999; **14:** 283–7.

Tooth erosion. The pH of some inhaled powder formulations of terbutaline, as well as of some corticosteroids, was found to be below 5.5, and it was suggested that this might contribute to the dissolution of enamel surfaces of teeth.[1] A later cohort study found no association between asthma and tooth erosion; however only about 10% of the medication prescribed for asthma in the cohort had a pH lower than 5.5.[2]

1. O'Sullivan EA, Curzon MEJ. Drug treatments for asthma may cause erosive tooth damage. *BMJ* 1998; **317:** 820.
2. Dugmore CR, Rock WP. Asthma and tooth erosion: is there an association? *Int J Paediatr Dent* 2003; **13:** 417–24.

Interactions

As for Salbutamol, p.1132.

Xanthines. The metabolic and cardiovascular responses to terbutaline infusion were significantly enhanced by *theophylline* in a study in 7 healthy subjects; in particular the fall in serum potassium was greater when both drugs were given.[1] Careful monitoring of serum potassium is recommended in severe asthma where theophylline and $beta_2$-agonists may be given together.

Terbutaline conversely has an effect on theophylline. Terbutaline can reduce serum-theophylline concentrations by increasing its systemic clearance. This may, or may not, have clinical implications, as improved clinical scores have still occurred with combined therapy despite the theophylline concentration being lower than when used alone; if respiratory symptoms persist, an increase in dosage may be contemplated while monitoring theophylline adverse effects and concentration.[2]

1. Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. *Br J Clin Pharmacol* 1986; **21:** 451–3.
2. Garty M, *et al.* Increased theophylline clearance in asthmatic patients due to terbutaline. *Eur J Clin Pharmacol* 1989; **36:** 25–8.

Pharmacokinetics

On inhalation of terbutaline, less than 10% of the drug is absorbed from the airways. The remainder is swallowed where it is variably absorbed from the gastrointestinal tract. Fasting bioavailability after oral doses is reported to be about 14 to 15% and is reduced by food. Terbutaline undergoes extensive first-pass metabolism by sulfate (and some glucuronide) conjugation in the liver and the gut wall. It is excreted in the urine and faeces partly as the inactive sulfate conjugate and partly as unchanged terbutaline, the ratio depending upon the route by which it is given. The terminal half-life after single and multiple dosing is reported to be between 16 and 20 hours. There is some placental transfer. Trace amounts are distributed into breast milk.

Stereoselectivity. Terbutaline, like many other sympathomimetics, exists in two stereoisomeric forms but only the (–)-enantiomer of terbutaline is pharmacologically active. Pharmacokinetic studies have been conducted on the two enantiomers and on the racemate.

The oral bioavailability of (–)-terbutaline was 14.8%, which was similar to that of the racemate; the bioavailability of (+)-terbutaline was much lower at 7.5%. The difference in bioavailability between the two enantiomers was mainly due to a difference in absorption (about 75% and 50% respectively) although a small difference in subsequent first-pass metabolism also occurred, with the (+)-isomer undergoing slightly more metabolism. It appeared that the (+)-isomer governed the elimination behaviour, both first-pass metabolism and renal clearance, of the racemate whereas the (–)-isomer determined the absorption.[1]

Other studies have also shown stereoselective sulfate conjugation of terbutaline with sulfation of the (+)-enantiomer being double that of the (–)-enantiomer.[2] The primary site of terbutaline sulfation for both enantiomers appears to be in the gut and is significantly correlated with the activity of catechol sulfotransferase.[3]

1. Borgström L, *et al.* Pharmacokinetic evaluation in man of terbutaline given as separate enantiomers and as the racemate. *Br J Clin Pharmacol* 1989; **27:** 49–56.
2. Walle T, Walle UK. Stereoselective sulphate conjugation of racemic terbutaline by human liver cytosol. *Br J Clin Pharmacol* 1990; **30:** 127–33.
3. Pacifici GM, *et al.* (+) and (–) terbutaline are sulphated at a higher rate in human intestine than in the liver. *Eur J Clin Pharmacol* 1993; **45:** 483–7.

Uses and Administration

Terbutaline sulfate is a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on $beta_2$ receptors (a $beta_2$ agonist). It has actions and uses similar to those of salbutamol (p.1133).

Terbutaline is given as the sulfate for its bronchodilating properties in reversible airways obstruction, as occurs in asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112). It also decreases uterine contractility and may be used to arrest premature labour (p.2003).

On inhalation, the bronchodilating effect of terbutaline usually begins within 5 minutes and lasts for up to 6 hours. The onset of action after oral doses is 30 to 45 minutes and its duration is up to 8 hours; the maximum effect occurs 1 to 4 hours after the dose.

Current asthma guidelines (see p.1108) recommend that inhaled short-acting $beta_2$ agonists such as terbutaline be used on an 'as-required', not regular, basis. In those patients requiring more than occasional use of terbutaline, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, terbutaline indicates deterioration of asthma control and the need for increased anti-inflammatory therapy.

- To relieve **acute bronchospasm** the usual dose is 1 or 2 inhalations of terbutaline sulfate 250 micrograms as required from a *metered-dose aerosol* every 4 to 6 hours, to a maximum of 8 inhalations in 24 hours.
- A breath-actuated metered-dose *powder inhaler* containing terbutaline sulfate is also available; one inhalation of 500 micrograms is taken when required up to a maximum of 6 inhalations in 24 hours.
- When inhalation is ineffective, terbutaline sulfate may be given *orally*; the usual initial dose is 2.5 or 3 mg three times daily increased up to 5 mg three times daily as necessary. Modified-release tablets are also available; the usual adult dose is 7.5 mg twice daily.
- Severe or unresponsive bronchospasm may require the use of terbutaline sulfate intermittently via a *nebuliser*. A usual dose is 5 to 10 mg inhaled 2 to 4 times daily. Single-dose units or a suitable dilution of a concentrated solution containing terbutaline sulfate 1% are used for this purpose.

Guidelines also allow for $beta_2$ agonists to be given more frequently or by continuous dosage at a higher rate in acute severe asthma (see under Asthma, p.1108).

- In the treatment of severe forms of bronchospasm, terbutaline sulfate may be given by subcutaneous, intramuscular, or slow intravenous *injection*; a dose of 250 to 500 micrograms may be given up to 4 times daily. Terbutaline sulfate may also be given by *intravenous infusion*, as a solution containing 3 to 5 micrograms/mL at a rate of 0.5 to 1 mL/minute.

Terbutaline sulfate is also used to arrest uncomplicated **premature labour** between 24 and 33 weeks of gestation. It is given by *intravenous infusion* in glucose 5%, preferably by syringe pump when the concentration is 100 micrograms/mL. If no syringe pump is available then the concentration of the infusion should be 10 micrograms/mL. The recommended initial rate of infusion is 5 micrograms/minute increased by 2.5 micrograms/minute at intervals of 20 minutes until contractions stop. Usually, a rate of up to 10 micrograms/minute is sufficient; rates in excess of 20 micrograms/minute should not be used and if that maximum rate does not delay labour then the infusion should be stopped. The maternal pulse should be monitored throughout the infusion which should be adjusted to avoid a maternal heart rate of more than 135 beats/minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema. Once contractions have ceased, the infusion should be given for 1 hour, then the dose may be decreased by 2.5 micrograms/minute at 20-minute intervals to the lowest maintenance dose that produces continued suppression of contractions. After a further 12 hours, *oral* maintenance therapy with 5 mg three times daily may be started. However, such usage is not recommended by the *BNF* as the risks to the mother (see Precautions under Salbutamol, p.1132) increase after 48 hours, and furthermore there is a lack of evidence of benefit from further treatment. *Subcutaneous* doses of 250 micrograms four times daily have been given for a few days before oral treatment was commenced.

For terbutaline sulfate doses used for bronchospasm in children, see Administration in Children, below.

Terbutaline in a bioadhesive vaginal gel is under investigation for the treatment of infertility linked to endometriosis.

Administration in children. To relieve **acute bronchospasm** in children, the *BNFC* recommends a dose of 500 micrograms of terbutaline sulfate, inhaled via a metered-dose *powder inhaler*, up to four times daily in children aged 5 years and over. *Oral* doses, although not recommended and unlicensed in the UK for children under 7 years of age, may be given in doses ranging from:

- 1 month to 7 years of age, 75 micrograms/kg (maximum dose 2.5 mg) three times daily
- 7 to 15 years of age, 2.5 mg two or three times daily
- over 15 years of age, as for adults (see Uses and Administration, above)

Severe or unresponsive bronchospasm may require the use of terbutaline sulfate inhaled via a *nebuliser*. UK licensed product information gives doses based on weight and age:

- under 3 years of age, average body-weight 10 kg, 2 mg given 2 to 4 times daily
- 3 to 5 years of age, average body-weight 15 kg, 3 mg given 2 to 4 times daily
- 6 to 7 years of age, average body-weight 20 kg, 4 mg given 2 to 4 times daily
- 8 years of age and over, body-weight greater than 25 kg, 5 mg given 2 to 4 times daily

In the treatment of severe forms of bronchospasm, terbutaline sulfate may be given by subcutaneous or slow intravenous *injection*; in children 2 years of age and over, the *BNFC* recommends a dose of 10 micrograms/kg given every 6 hours as required. A maximum single dose of 300 micrograms is recommended in children from 2 to 15 years of age, and in children over 15 years a maximum single dose of 500 micrograms is recommended.

Terbutaline sulfate may also be given by *intravenous infusion*; the *BNFC* recommends an initial dose of 2 to 4 micrograms/kg, then 1 to 10 micrograms/kg per hour according to response and heart rate. Although the injection is unlicensed in the UK for children under 2 years of age, the *BNFC* allows this dose for children from 1 month of age.

Cardiac disorders. A case report on the use of oral terbutaline for chronotropic support, in the setting of acute rejection after heart transplantation, found it to be effective and without any significant adverse effects.[1]

1. Coons JC, *et al.* Terbutaline for chronotropic support in heart transplantation. *Ann Pharmacother* 2004; **38:** 586–9.

Hypoglycaemia. Giving terbutaline 5 mg orally at night reduced the risk of nocturnal hypoglycaemia in a study in patients with type 1 diabetes.[1] A later study[2] reproduced these results in 21 patients with type 1 diabetes; however, hyperglycaemia was seen the next morning.

1. Saleh TY, Cryer PE. Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes Care* 1997; **20:** 1231–6.
2. Raju B, *et al.* Nocturnal hypoglycaemia in type 1 diabetes: an assessment of preventive bedtime treatments. *J Clin Endocrinol Metab* 2006; **91:** 2087–92.

Systemic capillary leak syndrome. Systemic capillary leak syndrome is a rare disorder marked by shifts of plasma from the intravascular to the extracellular space, and is often fatal. Acute attacks are treated with intravenous fluid resuscitation, but there is some anecdotal evidence that treatment with terbutaline combined with aminophylline or theophylline, both orally, may be useful in preventing further attacks.[1-3] Infusion of epoprostenol has also been used in acute management.[4]

1. Droder RM, *et al.* Control of systemic capillary leak syndrome with aminophylline and terbutaline. *Am J Med* 1992; **92:** 523–6.
2. Amoura Z, *et al.* Systemic capillary leak syndrome: report on 13 patients with special focus on course and treatment. *Am J Med* 1997; **103:** 514–19.
3. Tahirkheli NK, Greipp PR. Treatment of the systemic capillary leak syndrome with terbutaline and theophylline: a case series. *Ann Intern Med* 1999; **130:** 905–9.
4. Fellows IW, *et al.* Epoprostenol in systemic capillary leak syndrome. *Lancet* 1988; **ii:** 1143.

Urticaria. Patients with various types of urticaria unresponsive to conventional therapy with antihistamines (see p.1584) have obtained benefit from treatment with a combination of terbutaline and ketotifen; the urticarias have included chronic idiopathic urticaria,[1] dermographism,[1] and cold urticaria.[1,2] Terbutaline on its own was relatively ineffective and the mechanism of the combination was believed to be due to a stabilising effect on mast cells.[1]

Treatment of cold urticaria with a combination of terbutaline and aminophylline has also been studied.[3] The effectiveness of this combined therapy was reported to vary considerably between patients, but complete remission of the urticarial response was eventually seen in 37 of the 42 patients. Treatment was stopped in 3 patients in the first week due to cardiac adverse effects.

1. Saihan EM. Ketotifen and terbutaline in urticaria. *Br J Dermatol* 1981; **104:** 205–6.
2. Edge JA, Osborne JP. Terbutaline and ketotifen in cold urticaria in a child. *J R Soc Med* 1989; **82:** 439–40.
3. Husz S, *et al.* Treatment of cold urticaria. *Int J Dermatol* 1994; **33:** 210–13.

Preparations

BP 2008: Terbutaline Tablets;
USP 31: Terbutaline Sulfate Inhalation Aerosol; Terbutaline Sulfate Injection; Terbutaline Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Bricanyl; ***Austral.:*** Bricanyl; ***Austria:*** Bricanyl; ***Belg.:*** Bricanyl; ***Braz.:*** Bricanyl; Terbutil; ***Canad.:*** Bricanyl; ***Chile:*** Bricanyl†; ***Cz.:*** Bricanyl; ***Denm.:*** Bricanyl; ***Fin.:*** Bricanyl; ***Fr.:*** Bricanyl; ***Ger.:*** Aerodur; Arubendol†; Asthmoprotect†; Bricanyl; Butaliret†; Butalitab†; Contimit; Terbul; Terbuturmant†; ***Gr.:*** Bricanyl; Dracanyl; ***Hong Kong:*** Ataline; Bricanyl; Butylin†; Dhatalin;

Lanterbine; Terbron; Terbuta; Tolbin†; Vida-Butaline; ***Hung.:*** Bricanyl; ***India:*** Bricanyl; ***Indon.:*** Astherin; Brasmatic; Bricasma; Forasma; Lasmalin; Nairet; Pulmobron; Relivan; Sedakter; Tabas; Terasma; Tismalin; Yarisma; ***Irl.:*** Bricanyl; ***Israel:*** Bricalin; Terbulin; ***Ital.:*** Bricanyl; ***Malaysia:*** Ataline; Bricanyl; Bucanil; Butaline; Butanil†; Terbron†; Terbulin†; Tolbin; ***Mex.:*** Bricanyl†; Tazikén†; Terbuken; ***Neth.:*** Bricanyl; Terbasmin; ***Norw.:*** Bricanyl; ***NZ:*** Bricanyl; ***Philipp.:*** Alloxygen; Astebron; Bricanyl; Bronchodam; Pulmonyl; Pulmoxcel; 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; Bucaril; Cencanyl; Med-Broncodil†; Proasma-T; Sulterline; Terbron†; Terbulin; Terbuno; 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 Expectorant†; ***India:*** Ascoril +; Asmotone Plus; Bricarex; Bro-Zedex; Bronchosolvin; Cof QX; Grilinctus-BM; Mucaryl-AX†; Mucosol; Okaril Plus; Tergil; Tergil-T; Terpect; Terphylate; Terphylin; Theobric; Toscof; Tuspel Plus; ***Indon.:*** Bricasma Expectorant; Terasma Expectorant; ***Irl.:*** Bricanyl Expectorant; ***Mex.:*** Bricanyl EX; ***Philipp.:*** Bricanyl Expectorant; ***S.Afr.:*** Benylin Bronchospect; Bronchoped; Bronchospect†; ***Spain:*** Terbasmin Expectorante; ***Thai.:*** Bricanyl Expectorant†; Cofbron; Med-Broncodil Expectorant†; Terbosil†; Terbron Expectorant†; Tolbin.

Theobromine *(BAN)*

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

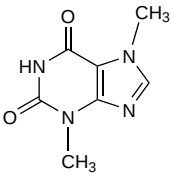
Теобромин

$C_7H_8N_4O_2$ = 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 (themisalum, 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.:*** Urodonal†.

Theophylline *(BAN)*

Anhydrous Theophylline; Teofilin; Teofilina; Teofilinas; Teofillin; Teofillina; Teofylliini; Teofyllin; Theofylin; Théophylline; Theophyllinum. 3,7-Dihydro-1,3-dimethylpurine-2,6(1*H*)-dione; 1,3-Dimethylxanthine.

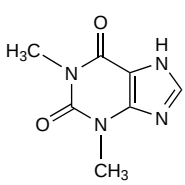
Теофиллин

$C_7H_8N_4O_2$ = 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 monohidrato; Teofilinas monohidratas; Teofylliinimonohydraatti; Teofyllinmonohydrat; Theofylin monohydrát; Theophylline Monohydrate; Théophylline monohydratée; Theophyllinum monohydricum.

Теофиллина Гидрат

$C_7H_8N_4O_2,H_2O$ = 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.[1] 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[2] 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.[1-3] 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.[1,2,4,5] Young infants and the elderly (over 60 years) appear to be at particular risk from chronic intoxication with theophylline.[6,7] 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.[5]

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.[1-3] Other toxic effects reported include dementia,[8] toxic psychosis,[9] symptoms of acute pancreatitis,[10] rhabdomyolysis[11-13] with associated renal failure,[11] and acute compartment syndrome.[14]

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[1] and prolonged monitoring of such patients is required. Patients have recovered despite serum-theophylline concentrations in excess of 200 micrograms/mL[12,14] but fatalities have occurred with much lower serum concentrations.[10,15,16] 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.[1,2] 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.[3]

1. Kearney TE, *et al.* Theophylline toxicity and the beta-adrenergic system. *Ann Intern Med* 1985; **102:** 766–9.
2. Shannon M. Hypokalemia, hyperglycemia 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[1] 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.[2] It is recommended[1] that plasma-potassium is monitored during intravenous theophylline therapy particularly if other drugs predisposing to hypokalaemia are also given (see also Interactions, below). Hypophosphataemia[1,3] and hyponatraemia[1] can also occur at therapeutic plasma-theophylline concentrations. Hypomagnesaemia[4] and hypercalcaemia[5] 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 hypercalcemia. *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[1] and in overdose.[2,3] Multifocal atrial tachycardia has also been associated with both theophylline overdose[2] and serum-theophylline concentrations within the generally accepted therapeutic range of 10