beta$_2$ agonists (on an as-required basis) and regular anti-inflammatory therapy should continue to be used.

Salmeterol is used in the form of the xinafoate; doses are expressed in terms of the equivalent amount of salmeterol; salmeterol xinafoate 1.45 micrograms is equivalent to about 1 microgram of salmeterol.

The usual dose is 50 micrograms of salmeterol twice daily from a metered-dose aerosol or dry powder inhaler; if necessary, up to 100 micrograms may be inhaled twice daily. For doses of salmeterol used in children, see Administration in Children, below.

◊ Reviews.

1. Meyer JM, *et al.* Salmeterol: a novel, long-acting beta -agonist. *Ann Pharmacother* 1993; **27:** 1478–87.
2. Bennett J, Tattersfield A. Drugs in focus: 15. Salmeterol. *Prescribers' J* 1995; **35:** 84–8.
3. Adkins JC, McTavish D. Salmeterol: a review of its pharmacological properties and clinical efficacy in the management of children with asthma. *Drugs* 1997; **54:** 331–54.
4. Jackson CM, Lipworth B. Benefit-risk assessment of long-acting β -agonists in asthma. *Drug Safety* 2004; **27:** 243–70.
5. Sovani MP, *et al.* A benefit-risk assessment of inhaled long-acting β -agonists in the management of obstructive pulmonary disease. *Drug Safety* 2004; **27:** 689–715.

Administration in children. For persistent reversible airways obstruction which requires regular bronchodilatation, including nocturnal asthma and prevention of exercise-induced asthma, children aged 4 to 12 years may be given 50 micrograms of salmeterol twice daily by inhalation.

Asthma. Salmeterol is a long-acting beta$_2$ agonist (duration of action about 12 hours). Guidelines on the management of asthma, see p.1108, generally recommend that salmeterol should be reserved for use in patients with chronic asthma who have already progressed to inhaled corticosteroids; it is not a substitute for corticosteroids. Evidence suggests that, apart from in severe exacerbations, adding a long-acting beta$_2$ agonist to standard dose inhaled corticosteroid therapy may be more effective than increasing the dose of corticosteroid, or than combining a corticosteroid and an anti-leukotriene drug. Salmeterol may also be useful in controlling persistent nocturnal asthma or preventing exercise-induced attacks. There is some evidence that after prolonged use, duration of protection against exercise-induced bronchoconstriction is reduced (see Tolerance, above).

References.

1. Lockey RF, *et al.* Nocturnal asthma: effect of salmeterol on quality of life and clinical outcomes. *Chest* 1999; **115:** 666–73.
2. Shrewsbury S, *et al.* Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 2000; **320:** 1368–73.
3. Holimon TD, *et al.* Nocturnal asthma uncontrolled by inhaled corticosteroids: theophylline or long-acting beta2 agonists. *Drugs* 2001; **61:** 391–418.
4. Johansson G, *et al.* Comparison of salmeterol/fluticasone propionate combination with budesonide in patients with mild-to-moderate asthma. *Clin Drug Invest* 2001; **21:** 633–42.
5. Heyneman CA, *et al.* Fluticasone versus salmeterol/low-dose fluticasone for long-term asthma control. *Ann Pharmacother* 2002; **36:** 1944–9.
6. Bateman ED, *et al.* Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004; **170:** 836–44.
7. Weiler JM, *et al.* Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. *Ann Allergy Asthma Immunol* 2005; **94:** 65–72.
8. Ni Chroinin M, *et al.* Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 15/01/08).
9. Gibson PG, *et al.* Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 15/01/08).
10. Masoli M, *et al.* Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005; **60:** 730–4.
11. Ducharme FM, *et al.* Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 15/01/08).
12. Walters EH, *et al.* Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 15/01/08).
13. The American Lung Association Asthma Clinical Research Centers. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007; **356:** 2027–39.

Chronic obstructive pulmonary disease. Short-acting beta$_2$ agonists are used as bronchodilators in patients with chronic obstructive pulmonary disease (see p.1112), although there is some evidence to suggest that an antimuscarinic might be preferable. Guidelines indicate that long-acting beta$_2$ agonists such as salmeterol may be used for maintenance therapy in moderate and more severe disease. Improvement in lung function and symptoms has been seen in such patients after regular treatment with inhaled salmeterol;[1-3] a reduction in exacerbations has also been seen.[4] Additional benefit has been reported from the use of salmeterol with inhaled corticosteroids.[5-7]

1. Boyd G, *et al.* An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1997; **10:** 815–21.
2. Mahler DA, *et al.* Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999; **115:** 957–65.
3. Stockley RA, *et al.* Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. *Thorax* 2006; **61:** 122–8.
4. Appleton S, *et al.* Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 15/01/08).
5. Calverley P, *et al.* Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; **361:** 449–56. Correction. *ibid.*; 1660.
6. Keating GM, McCormack PL. Salmeterol/fluticasone propionate: a review of its use in the treatment of chronic obstructive pulmonary disease. *Drugs* 2007; **67:** 2383–2405.
7. Kardos P, *et al.* Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; **175:** 144–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Abrilar†; Serevent; ***Austral.:*** Serevent; ***Austria:*** Serevent; ***Belg.:*** Serevent; ***Braz.:*** Serevent; ***Canad.:*** Serevent; ***Chile:*** Kolpovent†; Serevent; Xemos; ***Cz.:*** Serevent; ***Denm.:*** Serevent; ***Fin.:*** Serevent; ***Fr.:*** Serevent; ***Ger.:*** Aeromax; Serevent; ***Gr.:*** Serevent; ***Hong Kong:*** Serevent; ***Hung.:*** Serevent; ***India:*** Salmeter; Serobid; ***Indon.:*** Serevent; ***Irl.:*** Serevent; ***Israel:*** Serevent; ***Ital.:*** Arial; Salmetedur; Serevent; ***Jpn:*** Serevent; ***Malaysia:*** Serevent; ***Mex.:*** Serevent; ***Neth.:*** Serevent; ***Norw.:*** Serevent; ***NZ:*** Serevent; ***Philipp.:*** Serevent; ***Pol.:*** Serevent; ***Port.:*** Dilamax; Serevent; Ultrabeta; ***Rus.:*** Seretide (Серетид); Serevent (Серевент); ***S.Afr.:*** Serevent; ***Singapore:*** Serevent; ***Spain:*** Beglan; Betamican; Inaspir; Serevent; ***Swed.:*** Serevent; ***Switz.:*** Serevent; ***Thai.:*** Serevent; ***Turk.:*** Astmerole; Serevent; ***UK:*** Serevent; ***USA:*** Serevent; ***Venez.:*** Salmeter†; Salspray; Serevent.

Multi-ingredient: ***Arg.:*** Flutivent; Neumotide; Seretide; ***Austral.:*** Seretide; ***Austria:*** Seretide; Viani; ***Belg.:*** Seretide; ***Braz.:*** Seretide; ***Canad.:*** Advair; ***Chile:*** Aerometrol Plus; Aurituss; Brexotide; Seretide; ***Cz.:*** Duaspir; Seretide; ***Denm.:*** Seretide; ***Fin.:*** Seretide; ***Fr.:*** Seretide; ***Ger.:*** Atmadisc; Viani; ***Gr.:*** Seretide; Viani†; ***Hong Kong:*** Seretide; ***Hung.:*** Seretide; Thoreus; ***India:*** Forair; Seretide; Seroflo; ***Indon.:*** Seretide; ***Irl.:*** Seretide; ***Israel:*** Seretide; ***Ital.:*** Aliflus; Seretide; ***Malaysia:*** Seretide; ***Mex.:*** Seretide; ***Neth.:*** Seretide; Viani; ***Norw.:*** Seretide; ***NZ:*** Seretide; ***Philipp.:*** Seretide; ***Pol.:*** Seretide; ***Port.:*** Brisomax; Maizar; Seretaide; Veraspir; ***S.Afr.:*** Seretide; ***Singapore:*** Seretide; ***Spain:*** Anasma; Brisair; Inaladuo; Plusvent; Seretide; ***Swed.:*** Seretide; ***Switz.:*** Seretide; ***Thai.:*** Seretide; ***Turk.:*** Seretide; ***UK:*** Seretide; ***USA:*** Advair; ***Venez.:*** Seretide.

Seratrodast *(USAN, rINN)*

A-73001; AA-2414; Abbott-73001; ABT-001; Sératrodast; Seratrodastum. (±)-2,4,5-Trimethyl-3,6-dioxo-ζ-phenyl-1,4-cyclohexadiene-1-heptanoic acid.

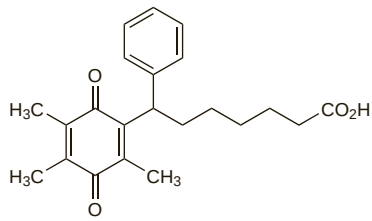
Сератродаст

$C_{22}H_{26}O_4$ = 354.4.

CAS — 112665-43-7; 103186-19-2.

ATC — R03DX06.

ATC Vet — QR03DX06.



Profile

Seratrodast is a thromboxane A_2 antagonist that is reported to reduce airway hyperresponsiveness. It is given orally in the prophylactic management of asthma (p.1108), in single doses of 80 mg in the evening after food.

Adverse effects include gastrointestinal disturbances, drowsiness, headache, palpitations, and hepatitis. Hepatic function should be monitored and the drug should be withdrawn if hypersensitivity reactions such as rashes and pruritus occur, or if there is elevation of liver enzyme values. Seratrodast should be used with care in patients with pre-existing hepatic impairment. It is not suitable for the treatment of an acute asthmatic attack.

◊ References.

1. Tamaoki J, *et al.* Effect of a thromboxane A antagonist on sputum production and its physicochemical properties in patients with mild to moderate asthma. *Chest* 2000; **118:** 73–9.

Preparations

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

Sodium Cromoglicate *(BANM, rINNM)*

Cromoglicate de Sodium; Cromoglicato de sodio; Cromoglicato disódico; Cromolyn Sodium *(USAN)*; Dinatrii Cromoglicas; Dinatrium-chromoglykát; Disodium Cromoglycate; FPL-670; Natrii cromoglicas; Natrio kromoglikatas; Natriumchromoglicat; Natriumkromoglikaatti; Natriumkromoglikat; Nátrium-kromoglikát; Sodium, cromoglicate de; Sodium Cromoglycate; Sodyum Kromoglikat. Disodium 4,4′-dioxo-5,5′-(2-hydroxytrimethylenedioxy)di(4*H*-chromene-2-carboxylate).

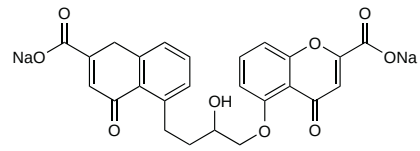
Натрий Кромоглициат

$C_{23}H_{14}Na_2O_{11}$ = 512.3.

CAS — 16110-51-3 (cromoglicic acid); 15826-37-6 (sodium cromoglicate).

ATC — A07EB01; D11AX17; R01AC01; R03BC01; S01GX01.

ATC Vet — QA07EB01; QD11AX17; QR01AC01; QR03BC01; QS01GX01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Sodium Cromoglicate). A white or almost white, hygroscopic, crystalline powder. Soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.
USP 31 (Cromolyn Sodium). A white, odourless, hygroscopic, crystalline powder. Soluble in water; insoluble in alcohol and in chloroform. Store in airtight containers.

Adverse Effects

Inhalation of sodium cromoglicate may cause transient bronchospasm, wheezing, cough, nasal congestion, and irritation of the throat. Nausea, headache, dizziness, an unpleasant taste, and joint pain and swelling have been reported. Other reactions include aggravation of existing asthma, urticaria, rashes, pulmonary infiltrates with eosinophilia, dysuria, and urinary frequency. Severe reactions such as marked bronchospasm, laryngeal oedema, angioedema, and anaphylaxis have been reported rarely.

Intranasal use of sodium cromoglicate may cause transient irritation of the nasal mucosa, sneezing, and occasionally epistaxis. Nausea, skin rashes, and joint pains have occurred when it is taken orally. Transient burning and stinging have occasionally been reported after use of sodium cromoglicate eye drops.

Formulation. Some of the adverse effects reported with sodium cromoglicate may be due to its formulation: there is a view that some of the irritant effects reported on inhalation may be due to the use of dry powder inhalers. It has also been suggested that in some patients receiving sodium cromoglicate via a nebuliser, hypotonicity of the nebuliser solution may induce bronchospasm,[1] although others consider this debatable.[2] Nausea, bloating, abdominal cramps, and flatulence developed in a 24-year-old lactase-deficient woman 2 hours after the use of sodium cromoglicate (*Intal*) inhalation capsules via a turbo-haler for exercise-induced asthma.[3] These symptoms recurred on rechallenge and were attributed to ingestion of lactose contained within the capsules.

1. Chin TW, Nussbaum E. Detrimental effect of hypotonic cromolyn sodium. *J Pediatr* 1992; **120:** 641–3.
2. Rachelefsky GS, *et al.* Detrimental effects of hypotonic cromolyn sodium. *J Pediatr* 1992; **121:** 992.
3. Brandstetter RD, *et al.* Lactose intolerance associated with Intal capsules. *N Engl J Med* 1986; **315:** 1613–14.

Precautions

Sodium cromoglicate has no role in the treatment of acute asthmatic attacks. Withdrawal of sodium cromoglicate may lead to recurrence of the symptoms of asthma. Should withdrawal be necessary it has been suggested that the dose be reduced gradually over a period of one week; patients in whom sodium cromoglicate therapy has permitted a reduction of corticosteroid dosage may require restoration of full corticosteroid cover.

Systemic corticosteroid therapy that has been reduced or stopped in asthmatic patients may need to be reinstated if symptoms increase, during periods of stress

such as infection, illness, trauma, or severe antigen challenge, or where airways obstruction impairs inhalation of sodium cromoglicate.

Pharmacokinetics

Sodium cromoglicate is poorly absorbed from the gastrointestinal tract, with a reported bioavailability of only 1%. It has been reported that on inhalation as a fine powder only about 8% of a dose is deposited in the lungs from where it is rapidly absorbed and excreted unchanged in the urine and bile. Less than 7% of an intranasal dose appears to be absorbed. The majority of an inhaled or an intranasal dose is swallowed and excreted unchanged via the gastrointestinal tract. About 0.03% of an ophthalmic dose is reported to be absorbed. The terminal elimination half-life has been reported to be about 20 minutes after intravenous dosage, but the elimination half-life after oral doses or inhalation is about 80 minutes.

◊ A study[1] in patients with exercise-induced asthma concluded that the plasma concentration of cromoglicate was almost certainly not related directly to its protective effect, although another study in asthmatic children given sodium cromoglicate by dry-powder inhalation, found both blood concentration and clinical response to be correlated with inhalation technique.[2]

1. Patel KR, *et al.* Plasma concentrations of sodium cromoglycate given by nebulisation and metered dose inhalers in patients with exercise-induced asthma: relationship to protective effect. *Br J Clin Pharmacol* 1986; **21:** 231–3.
2. Yahav Y, *et al.* Sodium cromoglycate in asthma: correlation between response and serum concentrations. *Arch Dis Child* 1988; **63:** 592–7.

Uses and Administration

Sodium cromoglicate is used for the prevention of allergic reactions. Although its precise mode of action remains uncertain, it is believed to act primarily by preventing release of mediators of inflammation from sensitised mast cells through stabilisation of mast-cell membranes. It has no direct antihistamine or anti-inflammatory action.

Sodium cromoglicate can prevent the asthmatic response to a variety of allergic and non-allergic stimuli. It is used in the management of chronic asthma that cannot be managed with inhaled $beta_2$ agonists alone; it is not used for acute attacks of asthma.

Sodium cromoglicate is also used in the prophylaxis and treatment of seasonal and perennial allergic rhinitis and allergic conditions of the eye including acute and chronic allergic conjunctivitis and vernal keratoconjunctivitis. It has been given orally, with dietary restriction, for the prevention of food allergies, and is also used in the treatment of mastocytosis.

It is important that the regular use of sodium cromoglicate is maintained, both in the prophylactic control of asthma and in the management of other allergic conditions. Beneficial effects may take several weeks to become established.

In the prophylaxis of **asthma**, sodium cromoglicate is given by inhalation either as a dry powder, or as a nebulised solution, or from a metered-dose aerosol. The usual dose as dry powder or nebulised solution is 20 mg by inhalation 4 times daily increased, if necessary, to 6 or 8 times daily. Once the asthma has been stabilised it may be possible to reduce the dosage. In different countries, sodium cromoglicate is available in different strengths of metered-dose aerosol. Using a metered-dose aerosol providing 5 mg per inhalation, the usual dose is 10 mg four times daily, increased to 6 to 8 times daily if necessary; it may be possible to reduce the dosage to 5 mg four times daily once the asthma has been stabilised. Additional doses as the aerosol or dry powder may be taken before exercise. Metered-dose aerosols providing 1 mg per inhalation are also available. The usual dose is 2 mg four times daily, which can be doubled if necessary. The adequacy of the lower dosage has been questioned (see under Administration, below).

Inhalation of sodium cromoglicate may cause bronchospasm; separate inhalation of a $beta_2$ agonist such as salbutamol a few minutes beforehand should prevent this. Use of a combination product containing a $beta_2$ agonist is not recommended as this is liable to be used inappropriately for relief of bronchospasm rather than for its prophylactic effect.

For the prophylaxis of **allergic rhinitis**, a 2 or 4% sodium cromoglicate solution can be given as a spray into both nostrils. The 2% spray contains about 2.5 mg per actuation and is given 4 to 6 times daily, and the 4% spray contains about 5 mg per actuation and is given 2 to 4 times daily. Prophylactic treatment for seasonal allergic rhinitis should begin 2 to 3 weeks before exposure to the offending allergen and should continue throughout the season. In **allergic conjunctivitis** and **vernal keratoconjunctivitis**, sodium cromoglicate is used as drops of 2 or 4%, applied 4 to 6 times daily.

In **food allergy** and in **mastocytosis**, sodium cromoglicate may be given in oral doses of 200 mg four times daily before meals. If satisfactory control is not achieved within 2 to 3 weeks the dosage may be doubled, but should not exceed 40 mg/kg daily; a reduction in dosage may be possible once symptoms have been controlled.

For details of doses in children, see Administration in Children below.

Action. Sodium cromoglicate has a range of actions at cellular level that may be important for its protective effect in asthma. It is known as a mast cell stabiliser that inhibits the release of histamine and other inflammatory mediators from sensitised mast cells. Other reported actions include a direct effect on airway nerves[1,2] and antagonism[3] of substance P, which ties up with its inhibition of the effects of platelet activating factor (PAF).[4,5]

There have been a few reports[6-8] of sodium cromoglicate producing bronchodilatation. However, in practice other drugs with accepted bronchodilating activity are used for this effect in asthma treatment schedules, see p.1108.

1. Barnes PJ. Asthma as an axon reflex. *Lancet* 1986; **i:** 242–5.
2. Dixon M, *et al.* The effects of sodium cromoglycate on lung irritant receptors and left ventricular cardiac receptors in the anaesthetized dog. *Br J Pharmacol* 1979; **67:** 569–74.
3. Page C. Sodium cromoglycate, a tachykinin antagonist? *Lancet* 1994; **343:** 70.
4. Morley J, *et al.* The platelet in asthma. *Lancet* 1984; **ii:** 1142–4.
5. Morley J. PAF and airway hyperreactivity: prospects for novel prophylactic anti-asthma drugs. In: *PAF, Platelets, and Asthma*, Basel, Birkhäuser Verlag, 1987: 87–95.
6. Horn CR, *et al.* Bronchodilator effect of disodium cromoglycate administered as a dry powder in exercise induced asthma. *Br J Clin Pharmacol* 1984; **18:** 798–801.
7. Weiner P, *et al.* Bronchodilating effect of cromolyn sodium in asthmatic patients at rest and following exercise. *Ann Allergy* 1984; **53:** 186–8.
8. Yuksel B, Greenough A. Bronchodilator effect of nebulized sodium cromoglycate in children born prematurely. *Eur Respir J* 1993; **6:** 387–90.

Administration. The effectiveness of sodium cromoglicate 2 mg four times daily by metered-dose aerosol inhaler has been reported by controlled studies in adults and children with asthma.[1-5] However, although sodium cromoglicate 2 mg by inhalation from a metered-dose aerosol was reported[6] to be as effective as 20 mg inhaled as powder, the tenfold difference in dosage has been questioned,[7] and others have reported contrary results.[8,9] It has been suggested that an aerosol supplying 5 mg per metered dose (see Uses and Administration, above) would be preferable.[10] In a comparison of single-dose pretreatment from metered-dose inhalers, sodium cromoglicate 10 mg (2 × 5 mg puffs) was as effective as beclometasone dipropionate 200 micrograms in inhibiting bronchial responsiveness to histamine.[11]

Care is required if inhaled sodium cromoglicate is given via a spacer device; evidence suggests that these may greatly influence the amount of drug delivered, reducing it to one-third of the dose delivered by inhaler actuation in some cases.[12]

1. Geller-Bernstein C, Levin S. Sodium cromoglycate pressurised aerosol in childhood asthma. *Curr Ther Res* 1983; **34:** 345–9.
2. Wheatley D. Sodium cromoglycate in aerosol form in regular users of bronchodilator drugs. *Curr Med Res Opin* 1983; **8:** 333–7.
3. Rubin AE, *et al.* The treatment of asthma in adults using sodium cromoglycate pressurized aerosol: a double-blind controlled trial. *Curr Med Res Opin* 1983; **8:** 553–8.
4. Blumenthal MN, *et al.* A multicenter evaluation of the clinical benefits of cromolyn sodium aerosol by metered-dose inhaler in the treatment of asthma. *J Allergy Clin Immunol* 1988; **81:** 681–7.
5. Selcow JE, *et al.* Clinical benefits of cromolyn sodium aerosol (MDI) in the treatment of asthma in children. *Ann Allergy* 1989; **62:** 195–9.
6. Latimer KM, *et al.* Inhibition by sodium cromoglycate of bronchoconstriction stimulated by respiratory heat loss: comparison of pressurised aerosol and powder. *Thorax* 1984; **39:** 277–81.
7. Anonymous. Sodium cromoglycate aerosol. *Drug Ther Bull* 1982; **20:** 27.
8. Robson RA, *et al.* Sodium cromoglycate: spincaps or metered dose aerosol. *Br J Clin Pharmacol* 1981; **11:** 383–4.
9. Bar-Yishay E, *et al.* Duration of action of sodium cromoglycate on exercise induced asthma: comparison of 2 formulations. *Arch Dis Child* 1983; **58:** 624–7.
10. Tullett WM, *et al.* Dose-response effect of sodium cromoglycate pressurised aerosol in exercise induced asthma. *Thorax* 1985; **40:** 41–4.
11. Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. *J Allergy Clin Immunol* 1987; **79:** 734–40.
12. Barry PW, O'Callaghan C. Inhalational drug delivery from seven different spacer devices. *Thorax* 1996; **51:** 835–40.

Administration in children. Children may be given sodium cromoglicate for prophylactic management of asthma and allergic rhinitis, and in the prophylaxis and treatment of acute and chronic allergic conjunctivitis and vernal keratoconjunctivitis, using adult doses, see Uses and Administration, above. Different countries may have different licensed lower age limits and some inhalation dosage forms are unsuitable in very young children.

In food allergy and in mastocytosis, sodium cromoglicate may be given orally to children from 2 years of age. A dose of 100 mg is given four times daily before meals. If satisfactory control is not achieved within 2 to 3 weeks the dosage may be doubled but should not exceed 40 mg/kg daily; a reduction in dosage may be possible once symptoms have been controlled. For food allergy, adult doses may be given to children from 14 years of age, and from 13 years for mastocytosis, see above.

Asthma. Sodium cromoglicate is used as a prophylactic agent in the management of chronic asthma (p.1108), but in practice inhaled corticosteroids are preferred if regular prophylactic treatment is indicated, i.e. if the condition cannot be managed with occasional use of an inhaled short-acting $beta_2$ agonist alone. Even in children, in whom cromoglicate has tended to be more widely used, inhaled corticosteroids are considered first-line preventers. A systematic review[1] comparing sodium cromoglicate with inhaled corticosteroids found that inhaled corticosteroids were superior in terms of asthma control and lung function for both children and adults with chronic asthma. However, guidelines still specify the use of cromoglicate or nedocromil as a valid alternative to inhaled corticosteroids in some circumstances.

Response to treatment with nebulised sodium cromoglicate was found to be age-related in a study of children under 2 years of age with recurrent or persistent wheezy bronchitis and a history of allergic symptoms.[2] It was effective in children of 12 to 24 months of age but not in those below 12 months. Similarly, nebulised sodium cromoglicate was no more effective than placebo in the treatment of a group of 31 infants with persistent wheezing aged under 1 year,[3] and long-term inhalation therapy was ineffective in children aged 1 to 4 years.[4]

1. Guevara JP, *et al.* Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 14/04/08).
2. Geller-Bernstein C, Levin S. Nebulised sodium cromoglycate in the treatment of wheezy bronchitis in infants and young children. *Respiration* 1982; **43:** 294–8.
3. Furfaro S, *et al.* Efficacy of cromoglycate in persistently wheezing infants. *Arch Dis Child* 1994; **71:** 331–4.
4. Tasche MJA, *et al.* Randomised placebo-controlled trial of inhaled sodium cromoglycate in 1-4-year-old children with moderate asthma. *Lancet* 1997; **350:** 1060–4. Correction. *ibid.* 1998; **351:** 376.

Cogan's syndrome. Sodium cromoglicate eye drops improved blurred vision in a patient who had had Cogan's syndrome (p.1502) for 18 years.[1] Sodium cromoglicate capsules [by mouth] also reduced the frequency of fever attacks in this patient.

1. Carter F, Nabarro J. Cromoglycate for Cogan's syndrome. *Lancet* 1987; **i:** 858.

Cough. Sodium cromoglicate has been used with modest success by aerosol inhalation to suppress the cough associated with ACE inhibitor therapy (p.1194) in some patients.[1,2] However, inhalation of nedocromil sodium was not helpful in the treatment of ACE inhibitor induced cough in 6 diabetic patients.[3] A systematic review[4] considered that there was no good evidence to support the use of inhaled cromoglicate or nedocromil in the treatment of non-specific cough in children.

1. Keogh A. Sodium cromoglycate prophylaxis for angiotensin-converting enzyme inhibitor cough. *Lancet* 1993; **341:** 560.
2. Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin-converting enzyme inhibitor cough. *Lancet* 1995; **345:** 13–16.
3. Puolijoki H, Rekiaro M. Lack of effect of nedocromil sodium in ACE-inhibitor-induced cough. *Lancet* 1995; **345:** 394.
4. Chang A, *et al.* Inhaled cromones for prolonged non-specific cough in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/08).

Eczema. Application of a 4% sodium cromoglicate lotion was found to be of benefit in improving symptoms and reducing topical corticosteroid use in a study[1] in children with moderately severe atopic dermatitis (p.1579).

1. Stainer R, *et al.* Efficacy and acceptability of a new topical skin lotion of sodium cromoglicate (Altoderm) in atopic dermatitis in children aged 2–12 years: a double-blind, randomized, placebo-controlled trial. *Br J Dermatol* 2005; **152:** 334–41.

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†.

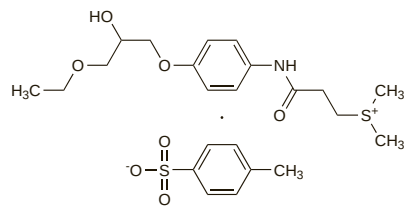
Suplatast Tosilate *(rINN)*

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.

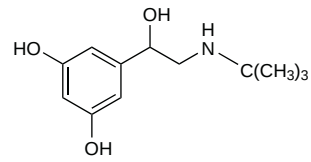
Тербуталина Сульфат

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