Agalsidase alfa and beta are recombinant forms of alpha galactosidase A used for the long-term enzyme replacement therapy of Fabry disease (see below).

Agalsidase alfa is given by intravenous infusion in a dose of 200 micrograms/kg over 40 minutes, repeated every alternate week.

Agalsidase beta is given by intravenous infusion in a dose of 1 mg/kg at an initial rate of no more than 250 micrograms/minute; the rate of administration may be gradually increased (by 50 to 80 micrograms/minute in each subsequent infusion) once tolerance has been established. The dose should be repeated every alternate week.

Fabry disease. Fabry disease (Anderson-Fabry disease) is a rare X-linked recessive lysosomal storage disorder.[1-6] It predominantly affects males, although female carriers may sometimes have clinical manifestations.[4,5] It is characterised by a deficiency of the enzyme alpha galactosidase A resulting in the intracellular accumulation of globotriaosylceramide (Gb_3) and other glycosphingolipids, especially in vascular endothelium and smooth muscle. Symptoms include severe neuropathies, fevers, skin blemishes (angiokeratomas), corneal and lenticular opacities, and gastrointestinal disturbances. Cardiac, cerebrovascular, and renal deterioration is progressive placing patients at increased risk for early-onset myocardial infarction, stroke, and renal failure.

Symptomatic treatment was the only option until the development of enzyme replacement therapy with agalsidase alfa[7] and beta.[8] Results from controlled studies show this form of therapy to be effective in clearing deposits from the kidneys, heart, and skin[9-12] as well as improving peripheral neuropathy.[13] An open-label extension study[14] of agalsidase beta in the 58 patients formerly studied in a 20-week controlled phase III study[11] confirmed the continued safety and efficacy of enzyme replacement therapy after 30 months of treatment. Benefit continued in these patients followed up for a further 24 months,[15] and kidney biopsies in 8 of the patients confirmed complete clearance of globotriaosylceramide. The cardiac effects of Fabry disease have been reviewed,[16] and both agalsidase alfa and beta have been reported to improve left ventricular structure and function, although further studies are required. Although most studies have been in adults, enzyme replacement therapy has been shown to be safe in children over 6 years of age.[17] Expert opinion generally recommends that treatment is begun as soon as clinical signs and symptoms are observed.[5,18] Gene therapy[19] is also under investigation.

1. Brady RO, Schiffmann R. Clinical features of and recent advances in therapy for Fabry disease. *JAMA* 2000; **284:** 2771–5.
2. Schiffmann R, Brady RO. New prospects for the treatment of lysosomal storage diseases. *Drugs* 2002; **62:** 733–42.
3. Mehta A. Agalsidase alfa: specific treatment for Fabry disease. *Hosp Med* 2002; **63:** 347–50.
4. Desnick RJ, *et al*. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Ann Intern Med* 2003; **138:** 338–46.
5. Desnick RJ, *et al*. Fabry disease in childhood. *J Pediatr* 2004; **144:** S20–S26.
6. Clarke JTR. Narrative review: Fabry disease. *Ann Intern Med* 2007; **146:** 425–33.
7. Beck M, *et al*. Fabry disease: overall effects of agalsidase alfa treatment. *Eur J Clin Invest* 2004; **34:** 838–44.
8. Keating GM, Simpson D. Agalsidase beta: a review of its use in the management of Fabry disease. *Drugs* 2007; **67:** 435–55.
9. Moore DF, *et al*. Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy. *Circulation* 2001; **104:** 1506–12.
10. Schiffmann R, *et al*. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 2001; **285:** 2743–9.
11. Eng CM, *et al*. Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med* 2001; **345:** 9–16.
12. Moore DF, *et al*. Elevated cerebral blood flow velocities in Fabry disease with reversal after enzyme replacement. *Stroke* 2002; **33:** 525–31.
13. Hilz MJ, *et al*. Enzyme replacement therapy improves function of C-, Aδ-, and Aβ-nerve fibers in Fabry neuropathy. *Neurology* 2004; **62:** 1066–72.
14. Wilcox WR, *et al*. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. *Am J Hum Genet* 2004; **75:** 65–74.
15. Germain DP, *et al*. Sustained, long-term renal stabilization after 54 months of agalsidase β therapy in patients with Fabry disease. *J Am Soc Nephrol* 2007; **18:** 1547–57.
16. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. *Heart* 2007; **93:** 528–35.
17. Ries M, *et al*. Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics* 2006; **118:** 924–32.
18. Banikazemi M, *et al*. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med* 2007; **146:** 77–86.
19. Siatskas C, Medin JA. Gene therapy for Fabry disease. *J Inherit Metab Dis* 2001; **24** (suppl 2): 25–41.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Replagal; ***Austria:*** Replagal; ***Belg.:*** Fabrazyme; Replagal; ***Canad.:*** Beano; Fabrazyme; Gaz Away; Replagal; ***Cz.:*** Fabrazyme; Replagal; ***Denm.:*** Fabrazyme; Replagal; ***Fin.:*** Fabrazyme; ***Fr.:*** Fabrazyme†; Replagal; ***Ger.:*** Fabrazyme; Replagal; ***Gr.:*** Fabrazyme; Replagal; ***Hung.:*** Fabrazyme; Replagal; ***Israel:*** Fabrazyme; Replagal; ***Ital.:*** Fabrazyme; Replagal; ***Jpn:*** Fabrazyme; ***Neth.:*** Fabrazyme; Replagal; ***Norw.:*** Fabrazyme; ***NZ:*** Fabrazyme; Replagal; ***Pol.:*** Fabrazyme; ***Port.:*** Fabrazyme; Replagal; ***Spain:*** Fabrazyme; Replagal; ***Swed.:*** Fabrazyme; ***Switz.:*** Fabrazyme; Replagal; ***UK:*** Beano; Fabrazyme; Replagal; ***USA:*** Beano; Fabrazyme.

Alpha$_1$-proteinase Inhibitor

Alpha$_1$ Antitrypsin; alpha-1-Antitrypsinum; Antitrypsine alpha-1; Inhibidor de la α_1- proteinasa.
ATC — B02AB02.
ATC Vet — QB02AB02.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Human α-1-Proteinase Inhibitor). A plasma protein fraction containing mainly human α-1-proteinase inhibitor. It is prepared from human plasma obtained from blood from healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. The method of preparation includes a step or steps that have been shown to remove or inactivate known agents of infection. Other plasma proteins may be present. Freeze-dried products are hygroscopic, white or pale yellow or pale brown powders or friable solids; liquid products are clear or slightly opalescent, colourless or pale yellow or pale green or pale brown. pH of 6.5 to 7.8. Store in airtight and sterile containers at a temperature not exceeding 25°.

Adverse Effects and Precautions

Adverse effects of intravenous alpha$_1$-proteinase inhibitor include asthenia, chills, increase in cough, dizziness, dyspnoea, flu-like symptoms, headache, hypotension, pain at the injection site, paraesthesias, pharyngitis, pruritus, rashes, somnolence, and tachycardia. The infusion should be interrupted or the rate reduced if adverse effects occur and resumed at a more tolerable rate once the symptoms have subsided; the infusion should be stopped immediately in the event of anaphylactic or anaphylactoid reactions, and full supportive measures implemented. Preparations derived from pooled human plasma carry a risk of transmission of infection (see Blood, p.1056).

The drug is contra-indicated in patients with selective IgA deficiencies who have known antibody against IgA since they are at risk of severe reactions to IgA that may be present in the product.

Uses and Administration

Endogenous alpha$_1$-proteinase inhibitor is a serum glycoprotein synthesised in the liver that acts as an elastase inhibitor, primarily inhibiting neutrophil elastase. Alpha$_1$-proteinase inhibitor, prepared from pooled human plasma, is used as replacement therapy in patients with emphysema who have congenital alpha$_1$ antitrypsin deficiency (see below). It is given in a dose of 60 mg/kg once a week by intravenous infusion at a rate of about 0.08 mL/kg per minute (usually corresponding to a 15 to 30 minute infusion).

A recombinant form of alpha$_1$-proteinase inhibitor is under investigation for nebulised delivery in congenital alpha$_1$ antitrypsin deficiency and cystic fibrosis (see below).

Alpha$_1$-proteinase inhibitor has also been investigated for the prevention of bronchopulmonary dysplasia (p.1500) in preterm neonates.

Alpha$_1$ antitrypsin deficiency. Alpha$_1$ antitrypsin deficiency (alpha$_1$-proteinase inhibitor deficiency) is characterised by chronic obstructive pulmonary disease (COPD) and chronic liver disease associated with a lack of alpha$_1$-proteinase inhibitor.[1] This inhibitor is produced in the liver but exerts its main effects in the lungs as an inhibitor of neutrophil elastase, an enzyme released in response to inflammation. Congenital deficiency of the inhibitor thus leaves the lungs vulnerable to destruction by elastase, leading to the development of emphysema (see Chronic Obstructive Pulmonary Disease, p.1112), usually in the third or fourth decade of life. Hepatic manifestations of deficiency include hepatitis, cirrhosis, and hepatoma. Panniculitis and vasculitis may also occur less frequently in some phenotypes.[2,3]

Management of COPD associated with the deficiency involves avoidance of factors (mainly cigarette smoking) that cause pulmonary inflammation, and supportive treatment with bronchodilators and oxygen as appropriate. Augmentation therapy with alpha$_1$-proteinase inhibitor to raise serum concentrations above the protective threshold is also of benefit in some patients.[2,4] Intravenous infusion of the drug has been shown to correct the biochemical abnormality[5] and has been recommended in those patients with some deterioration of lung function.[2,6] In a short-term study[7] serum and secretion concentrations of alpha$_1$-proteinase inhibitor as well as markers of neutrophilic inflammation were monitored in 12 patients receiving augmentation therapy over 4 weeks. Results demonstrated a rise in serum levels of alpha$_1$-proteinase inhibitor to above the protective threshold, and reduction in elastase activity and levels of leukotriene B_4 levels (thought to be important in producing airway inflammation in alpha$_1$ antitrypsin deficiency). A small placebo-controlled study[8] found that the rate of decline of FEV_1 was not affected in patients treated for at least 3 years. Data[9] from a large registry of patients also suggested that, overall, treatment did not affect the rate of decline of FEV_1, but that it decreased mortality, although this may be influenced by other factors. Evaluation[6] of 2 of these studies[8,9] and one other concluded that replacement therapy might reduce the progression of disease in selected patients, but that further randomised placebo-controlled studies were required to provide conclusive evidence for overall clinical efficacy. The Canadian Thoracic Society[10] recommends that replacement therapy should be reserved for patients with an FEV_1 between 35 and 65% predicted who are no longer smoking and on optimal medical therapy but continuing to show a rapid decline in FEV_1. In a retrospective cohort study[11] in 96 patients followed up for a minimum of 12 months, results indicated that the rate of progression of pulmonary emphysema was reduced during the time that the patients received augmentation therapy, and patients with well-maintained lung function and a rapid decline in FEV_1 benefited most from therapy. These authors recommended early diagnosis to identify patients at risk and to start augmentation even if lung function is greater than 65% predicted.

Liver involvement does not respond to treatment with alpha$_1$-proteinase inhibitor and is managed symptomatically.[2]

Several new approaches to treatment of alpha$_1$ antitrypsin deficiency are under investigation:[2,3,12] plasma-derived and recombinant forms of alpha$_1$-proteinase inhibitor for inhalation; synthetic elastase inhibitors for oral use; synthetic chaperones to block intrahepatic polymerisation of the inhibitor and other methods to improve serum concentrations; retinoids; inhaled hyaluronic acid; and gene therapy.

1. Köhnlein T, Welte T. Alpha-1 antitrypsin deficiency: pathogenesis, clinical presentation, diagnosis, and treatment. *Am J Med* 2008; **121:** 3–9.
2. American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003; **168:** 818–900. Also available at: http://www.thoracic.org/sections/publications/statements/pages/respiratory-disease-adults/alpha1.html (accessed 14/07/06)
3. Stoller JK, Aboussouan LS. α -Antitrypsin deficiency. *Lancet* 2005; **365:** 2225–36.
4. Juvelekian GS, Stoller JK. Augmentation therapy for α -antitrypsin deficiency. *Drugs* 2004; **64:** 1743–56.
5. Coakley RJ, *et al*. α1-Antitrypsin deficiency: biological answers to clinical questions. *Am J Med Sci* 2001; **321:** 33–41.
6. Abboud RT, *et al*. Alpha -antitrypsin deficiency: a position statement of the Canadian Thoracic Society. *Can Respir J* 2001; **8:** 81–8.
7. Stockley RA, *et al*. The effect of augmentation therapy on bronchial inflammation in α1-antitrypsin deficiency. *Am J Respir Crit Care Med* 2002; **165:** 1494–8.
8. Dirksen A, *et al*. A randomized clinical trial of α -antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999; **160:** 1468–72.
9. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV decline in individuals with severe deficiency of α -antitrypsin. *Am J Respir Crit Care Med* 1998; **158:** 49–59.
10. O'Donnell DE, *et al*. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2007 update. *Can Respir J* 2007; **14** (suppl B): 5B–32B.
11. Wencker M, *et al*. Longitudinal follow-up of patients with α -protease inhibitor deficiency before and during therapy with IV α -protease inhibitor. *Chest* 2001; **119:** 737–44.
12. Sandhaus RA. α -Antitrypsin deficiency 6: new and emerging treatments for α -antitrypsin deficiency. *Thorax* 2004; **59:** 904–9.

Cystic fibrosis. Some of the inflammatory damage that occurs in the lungs of patients with cystic fibrosis is thought to be caused by excessive amounts of elastase released locally. Alpha$_1$-proteinase inhibitor given by nebuliser is therefore under investigation[1-3] in patients with cystic fibrosis (p.166).

1. Martin SL, *et al*. Safety and efficacy of recombinant alpha -antitrypsin therapy in cystic fibrosis. *Pediatr Pulmonol* 2006; **41:** 177–83.
2. Cantin AM, *et al*. Prolastin aerosol therapy and sputum taurine in cystic fibrosis. *Clin Invest Med* 2006; **29:** 201–7.
3. Griese M, *et al*. α -Antitrypsin inhalation reduces airway inflammation in cystic fibrosis patients. *Eur Respir J* 2007; **29:** 240–50.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Prolastin; ***Canad.:*** Prolastin; ***Cz.:*** Trypsone; ***Fr.:*** Alfalastin; ***Ger.:*** Prolastin; ***Ital.:*** Prolastina; ***Port.:*** Prolastin; ***Spain:*** Prolastina; Trypsone; ***USA:*** Aralast; Prolastin; Zemaira.

Althaea

Altea; Alteablad (marshmallow leaf); Altearot (marshmallow root); Alteeanjuuri (marshmallow root); Alteeanlehti (marshmallow leaf); Alteia; Alth.; Althaea folium (marshmallow leaf); Althaeae radix (marshmallow root); Eibisch; Guimauve; Guimauve, feuille de (marshmallow leaf); Guimauve, racine de (marshmallow root); Korzeń prawoślazu (marshmallow root); Liść prawoślazu (marshmallow leaf); Malvavisco; Marshmallow; Orvosizilíz-gyökér (marshmallow root); Orvosizilíz-levél (marshmallow leaf); Proskurníkový kořen (marshmallow root); Proskurníkový list (marshmallow leaf); Svilarožių lapai (marshmallow leaf); Svilarožių šaknys (marshmallow root).
ATC — R05CA05.
ATC Vet — QR05CA05.

Pharmacopoeias. *Eur.* (see p.vii) includes the root and the leaf. *Fr.* also includes the flower.
Ph. Eur. 6.2 (Marshmallow Root; Althaeae Radix). The peeled or unpeeled, whole or cut, dried root of marshmallow, *Althaea officinalis*. Protect from light.
Ph. Eur. 6.2 (Marshmallow Leaf; Althaea Folium). The whole or cut dried leaf of *Althaea officinalis*. Protect from light.

Profile

Althaea is demulcent and emollient and has been used for irritation and inflammation of the mucous membranes of the mouth and pharynx, and relief of associated dry cough. It has also been used in traditional remedies for a variety of disorders including gastrointestinal disturbances.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Primadrill; ***Ger.:*** Phytohustil; ***Pol.:*** Althagem; Althamel; Rubital.

Multi-ingredient: ***Austral.:*** Althaea Complex; Cough Relief†; Garlic and Horseradish + C Complex; Hydrastis Complex†; ***Austria:*** Heumann's Bronchialtee; Paracodin; The Chambard-Tee; Tuscalman; ***Belg.:*** Sedemol; Sulfa-Sedemol; ***Braz.:*** Peitoral Angico Pelotense†; ***Canad.:*** Original Herb Cough Drops; Swiss Herb Cough Drops; ***Cz.:*** Detska Cajova Smes; Detsky Caj s Hermankem; Nontusyl†; Prudušková; Pulmoran; Species Pectorales Planta; ***Fr.:*** Apilaxe†; Mediflor Tisane No 4 Diuretique; Pansoral Premieres Dents; ***Ger.:*** Em-eukal Husten- und Brusttee†; Heumann Bronchialtee Solubifix T; Junisana†; Tonsilgon; ***Indon.:*** Silex; ***Ital.:*** Altea (Specie Composta)†; Altuss; Gastrotuss; ***Malaysia:*** Horseradish Plus†; ***Pol.:*** Rubital Compositum; Syrop Prawoslazowy Zlozony; Tabulettae Laxantes; ***Rus.:*** Linkus (Линкас); Pansoral Teething (Пансорал Первые Зубы); Tonsilgon N (Тонзилгон Н); ***S.Afr.:*** Cough Elixir; ***Singapore:*** Pansoral Teething; ***Spain:*** Bronpul†; Llantusil†; Malvaliz†; Natusor Broncopul†; Natusor Farinol†; Natusor Gastrolen†; Natusor Malvasen†; Senalsor†; ***Switz.:*** Malveol; Neo-DP†; Tisane pectorale et antitussive; Tisane pectorale pour les enfants; Tisane Provencale No 1; Tuscalman; ***UK:*** Herb and Honey Cough Elixir; Herbheal Ointment; Modern Herbals Cold & Catarrh; Potter's Catarrh Pastilles; Sinotar; ***Venez.:*** Novacodin.

Alum

Alaun; Allume; Aluin; Alumbre; Alumen; Aluminium Kalium Sulfuricum; Aluminium Potassium Sulphate; Alumínium-káliumszulfát; Alun; Aluna; Alūnas; E522; Glinowo-potasowy siarczan; Glinu potasu siarczan; Kalii Aluminii Sulfas Dodecahydricus; Potash Alum; Potassium Alum; Síran draselno-hlinitý dodekahydrát.

Potassium aluminium sulphate dodecahydrate.

$AlK(SO_4)_2.12H_2O$ = 474.4.

CAS — 7784-24-9 (alum dodecahydrate); 10043-67-1 (anhydrous alum).

ATC — S01XA07.

ATC Vet — QS01XA07.

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

US also includes dodecahydrated ammonia alum (Ammonium Alum). *Jpn* also includes dried alum.

Ph. Eur. 6.2 (Alum). Colourless, transparent, crystalline masses or a granular powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol; soluble in glycerol. A 10% solution in water has a pH of 3.0 to 3.5.

USP 31 (Potassium Alum). A white powder or large, colourless crystals or crystalline fragments. It is odourless. Soluble 1 in 7 of water and 1 in 0.3 of boiling water; insoluble in alcohol; freely but slowly soluble in glycerol. Its solutions are acid to litmus. Store in airtight containers.

Adverse Effects

Large doses of alum are irritant and may be corrosive; gum necrosis and gastrointestinal haemorrhage have occurred. Systemic absorption from bladder irrigation solutions can cause acute aluminium toxicity (see under Aluminium below) including encephalopathy.

◊ Acute encephalopathy has been reported[1,2] after bladder irrigation with alum solutions in the treatment of bladder haemorrhage. Anecdotal evidence would suggest that this practice should be avoided in patients with renal insufficiency.[1]

1. Phelps KR, *et al.* Encephalopathy after bladder irrigation with alum: case report and literature review. *Am J Med Sci* 1999; **318:** 181–5.
2. Nakamura H, *et al.* Acute encephalopathy due to aluminium toxicity successfully treated by combined intravenous deferoxamine and hemodialysis. *J Clin Pharmacol* 2000; **40:** 296–300.

Uses and Administration

Alum precipitates proteins and is a powerful astringent. It is often included in preparations used as mouthwashes or gargles and in dermatological preparations.

Alum, either as a solid or as a solution, may be used as a haemostatic. Intravesical instillation of alum, typically as a 1% solution, has been used as a treatment for haemorrhagic cystitis (p.2178).

Alum is also used as a mordant in the dyeing industry.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Citramin†.

Multi-ingredient: ***Arg.:*** Bentophyto; ***Austria:*** EST; ***Braz.:*** Lucretin; ***Canad.:*** Fletchers Sore Mouth Medicine; ***Ger.:*** Retterspitz Ausserlich; Retterspitz Innerlich; ***India:*** Feel Chill; ***Ital.:*** Lavanda Sofar; ***Mex.:*** Forcremol; ***Neth.:*** Trachitol; ***NZ:*** Grans Remedy; ***Spain:*** Co Bucal; Lindemil; ***USA:*** BFI; Massengill; Mycinette; ***Venez.:*** Borogin.

Aluminium

Aluminio; Aluminum; E173; Glin.

Al = 26.9815386.

CAS — 7429-90-5.

Description. Aluminium is a malleable and ductile soft silvery-white metal, becoming coated with a thin layer of oxide.

Pharmacopoeias. *Br.* includes Aluminium Powder.

BP 2008 (Aluminium Powder). An odourless or almost odourless, silvery-grey powder. It consists mainly of metallic aluminium in very small flakes, usually with an appreciable quantity of aluminium oxide. It is lubricated with stearic acid to protect the metal from oxidation. Practically insoluble in water and in alcohol; it dissolves in dilute acids and in aqueous solutions of alkali hydroxides, with the evolution of hydrogen.

Handling. Aluminium powder has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Incompatibility. Incompatibilities have been reported between aluminium in injection equipment and metronidazole,[1,2] and between aluminium and various antineoplastics including cisplatin, daunorubicin, and doxorubicin.[3-6] The suitability of aluminium caps for sugar-containing liquids has also been questioned. Abrasion of the aluminium cap by sugar from *Ceporex Syrup* [cefalexin] has resulted in the formation of a black slime.[7]

1. Schell KH, Copeland JR. Metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 1040, 1042.
2. Struthers BJ, Parr RJ. Clarifying the metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 2660.
3. Bohart RD, Ogawa G. An observation on the stability of cis-dichlorodiammineplatinum (II): a caution regarding its administration. *Cancer Treat Rep* 1979; **63:** 2117–18.
4. Gardiner WA. Possible incompatibility of doxorubicin hydrochloride with aluminum. *Am J Hosp Pharm* 1981; **38:** 1276.
5. Williamson MJ, *et al.* Doxorubicin hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1983; **40:** 214.
6. Ogawa GS, *et al.* Dispensing-pin problems. *Am J Hosp Pharm* 1985; **42:** 1042.
7. Tressler LJ. Medicine bottle caps. *Pharm J* 1985; **235:** 99.

Adverse Effects, Treatment, and Precautions

Aluminium toxicity is well recognised in patients with renal impairment. Patients undergoing dialysis have experienced encephalopathy, osteodystrophy, and anaemia associated with an aluminium salt taken as a phosphate binder or with aluminium present in the water supply. For this reason, aluminium-free phosphate binders are often used in dialysis patients and the concentration of aluminium in dialysis fluid has been limited to not more than 10 micrograms/litre (see Aluminium Overload under Dialysis Solutions, p.1671). Serum-aluminium concentrations should be monitored regularly in patients undergoing dialysis.

Aluminium toxicity has followed the use of parenteral fluids and infant feeds with a high concentration of aluminium.

Aluminium toxicity may be treated by removal of the aluminium with desferrioxamine (p.1441).

The adverse effects of aluminium salts and precautions to be observed are described under Aluminium Hydroxide, p.1706.

◊ A review of aluminium toxicity[1] lists possible sources of aluminium including water, antacids, phosphate-binding gels, total parenteral nutrition solutions, processed human serum albumin, fluids used in infants, and environmental pollution; cooking utensils and beverages such as tea have also been suggested as possible sources of aluminium. It has been suggested that over-the-counter preparations of antacids, which can contain significant amounts of aluminium, represent the most important quantitative source of aluminium exposure.[2] Toxicity tends to occur when the gastrointestinal barrier to aluminium absorption is circumvented, as in intravenous fluid use or dialysis, or if the excretion of aluminium is reduced, as in renal impairment. Infants, especially preterm infants, form a special risk group.[3-6]

Accidental deposition of 20 tonnes of aluminium sulfate in a reservoir in Cornwall, UK in 1988 led to contamination of a nearby town's water supply.[7] Symptoms reported included diarrhoea, mouth ulcers or blisters, malaise, joint symptoms (mainly deterioration of existing symptoms), and memory defects (usually beginning 2 to 3 months after the incident). Although some medical experts considered that no long-term toxic effects were to be expected,[7] aluminium deposits were found in the bones of 2 individuals 6 to 7 months later.[8] In a study[9] undertaken 3 years after the incident, 55 adults who claimed to have suffered cerebral damage performed poorly in psychomotor testing. The authors attributed this to aluminium exposure, but the study's design and conclusions have been criticised.[10-12] An inquiry by the UK DoH[13] does not anticipate that exposure to aluminium from this incident would have caused long-term health problems in people who were adults or toddlers at the time, although this possibility should be explored further in those who were bottle-fed infants (i.e. below one year of age) at that time. Further studies have also been recommended on the neuropsychological status and prevalence of joint problems in the population who consumed the contaminated water.

1. Monteagudo FSE, *et al.* Recent developments in aluminium toxicology. *Med Toxicol* 1989; **4:** 1–16.
2. Reinke CM, *et al.* Aluminium in over-the-counter drugs: risks outweigh benefits? *Drug Safety* 2003; **26:** 1011–25.
3. Bishop N, *et al.* Aluminium in infant formulas. *Lancet* 1989; **i:** 490.
4. Lawson M, *et al.* Aluminium and infant formulae. *Lancet* 1989; **i:** 614–15.
5. Anonymous. Aluminium content of parenteral drug products. *WHO Drug Inf* 1990; **4:** 70.
6. American Academy of Pediatrics Committee on Nutrition. Aluminum toxicity in infants and children. *Pediatrics* 1996; **97:** 413–16.
7. Anonymous. Camelford two years on. *Lancet* 1990; **336:** 366.
8. Eastwood JB, *et al.* Aluminium deposition in bone after contamination of drinking water supply. *Lancet* 1990; **336:** 462–4.
9. Altmann P, *et al.* Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident. *BMJ* 1999; **319:** 807–11.
10. David A. Cerebral dysfunction after water pollution incident in Camelford: results were biased by self selection of cases. *BMJ* 2000; **320:** 1337.
11. Esmonde TFG. Cerebral dysfunction after water pollution incident in Camelford: study has several methodological errors. *BMJ* 2000; **320:** 1337–8.
12. McMillan TM. Cerebral dysfunction after water pollution incident in Camelford: study may prolong the agony. *BMJ* 2000; **320:** 1338.
13. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Subgroup Report on the Lowermoor Water Pollution Incident. DoH (issued 26th January, 2005). Available at: http://www.advisorybodies.doh.gov.uk/cotnonfood/lsgreportjan05.pdf (accessed 04/04/08)

Burns. Thermal burns have been reported in patients undergoing magnetic resonance imaging (MRI) procedures when wearing transdermal medication patches containing aluminium in the backing material.[1] Aluminium is a conductive material and could induce a concentration of electrical currents sufficient to cause serious burns if placed in the MRI field; a similar phenomenon could also occur with external defibrillation.

1. Health Canada. Association of transdermal drug patches with thermal burns during magnetic resonance imaging procedures (issued 26th April 2005). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/mri-irm_patch-timbre_nth-ah_e.pdf (accessed 03/04/08)

Effects on mental function. Encephalopathy with seizures has been associated with the use of aluminium-containing materials used for bone reconstruction.[1,2] In each case, reconstruction of areas of the skull resulted in high concentrations of aluminium in the CSF.

1. Renard JL, *et al.* Post-otoneurosurgery aluminium encephalopathy. *Lancet* 1994; **344:** 63–4.
2. Hantson P, *et al.* Encephalopathy with seizures after use of aluminium-containing bone cement. *Lancet* 1994; **344:** 1647.

ALZHEIMER'S DISEASE. The role of aluminium in the aetiology of Alzheimer's disease (see Dementia, p.362) is, at best, unclear.[1-4] Circumstantial evidence of a positive association arises from *animal* and *in-vitro* data, together with clinical observations that aluminium is present in senile plaques and neurofibrillary tangles occurring in Alzheimer's disease, that giving aluminium chelators to Alzheimer patients may slow the progression of the disease, and that the risk of brain changes is increased in people living in areas with a high aluminium content in the drinking water supply. Some of these findings have been criticised, disproved, or not confirmed by other workers. Listed below are some of the studies which point to an association between aluminium intake and Alzheimer's disease,[5-8] some criticisms,[9-13] and some negative findings.[14,15]

There does not appear to be a risk of aluminium accumulation from normal use of aluminium-containing antacids by patients with normal renal function; consequently use of these antacids by such patients should not be considered to put them at risk of Alzheimer's disease.[16,17]

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15. Wettstein A, *et al.* Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water. *Int Arch Occup Environ Health* 1991; **63:** 97–103.
16. Anonymous. Aluminium salts and Alzheimer's disease. *Pharm J* 1991; **246:** 809.
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Uses and Administration

Aluminium is used in packaging and in injection equipment. The foil is also used as a dressing and for insulation. Aluminium may also be employed as a colouring agent for some foodstuffs. Aluminium powder alone and in paste form with zinc oxide has been used as a dressing. Astringent aluminium salts are used as antiperspirants. Aluminium hydroxide (p.1706) is used as an antacid.

Aluminium oxide (p.1585) has been used as an abrasive agent.