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.

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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.

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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).

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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.