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Diagnostic use. Sensitivity testing can be used to confirm that suspected allergens are mainly responsible for the symptoms of a suspected hypersensitivity reaction. It is necessary before patients with allergies are managed either by allergen avoidance or treated with allergen immunotherapy (see above). However, sensitivity testing should not form the sole basis of the treatment of hypersensitivity reactions.

Type IV (delayed) hypersensitivity reactions such as contact dermatitis are normally diagnosed using patch tests. A number of standard techniques are available, but in general they all involve maintaining a standard amount of the test substance in contact with the skin for 48 to 72 hours. A positive response is shown by erythema, swelling, or vesiculation. The sensitivity of different parts of the body varies, and this should be accounted for in applying test substances and controls. The test results are normally read 30 to 60 minutes after removal of the patches to allow any pressure effects of the patches to subside. Patch testing with mixtures of allergens may be necessary to diagnose contact dermatitis in patients hypersensitive to multiple allergens.

Type I (immediate) hypersensitivity reactions such as allergic rhinitis, allergic asthma, and insect-sting hypersensitivity are tested using skin-prick or intradermal tests. Since the allergen is

introduced through the skin in these tests, the risk of systemic reactions is greater than patch testing, and adrenaline injection should be kept available. The skin-prick test involves pricking the epidermis through a drop of allergen in solution, and comparing the result after 15 to 20 minutes with positive and negative controls. This test is inexpensive and the results available rapidly. The intradermal (intracutaneous) test is used if the skin-prick test result does not agree with a strong clinical suspicion, although now that potent allergen extracts are used for skin-prick tests, the intradermal test offers few advantages and has greater risk of systemic reactions. Skin testing is unreliable for evaluating hypersensitivity to drugs, except for penicillins and for certain macromolecules. Skin test titration, that is testing with a series of dilutions, has been used to determine a safe starting dose for allergen immunotherapy.

Provocation tests are designed to reproduce symptoms of hypersensitivity by controlled exposure to a suspected allergen. They are used when skin or laboratory tests are unavailable, or IgE is not involved in the mechanism. Provocation may be by the bronchial, oral, nasal, or ocular routes. Facilities for full cardiopulmonary resuscitation should be immediately available.

In-vitro methods for measuring antigen-specific IgE include immunoassays such as the enzyme-linked immunosorbent assay (ELISA), which has now replaced the radioallergosorbent test (RAST). These tests can be used in place of skin-prick tests but they are expensive and the results not available as quickly.

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Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Albay; Allpyral; **Belg.**: Alyostal; Phargalgen; Pollinex†; **Braz.**: Nikkho Vac; **Canada.**: Pollinex-R; **Cz.**: Alutard SQ; Alyostal; APSI/AQ†; ASD†; D-Ak; Grazax; H-Ak; Pangramin; Pollinex; Soluprick SQ; Staloral; **Denm.**: Alutard SQ; Aquagen SQ; Phargalgen; Sensitiner; Soluprick SQ; True Test; **Fr.**: Albe; Alyostal; ASD†; Dialertest; **Ger.**: ALK; Allergovit; Depot-Hal; Novo-Helisen; Oralvac; Phostal; Pollinex Quattro; Pollinose S†; Purethal; Reless; Staloral; TA Baume; TA Graser; TA MIX; Tol; Tyrosin TU; Venomahal; Venomil; **Hung.**: Lais; Pangramin; Purethal; Venomahal; **Israel.**: True Test; **Ital.**: Phostal; Staloral; **Mex.**: True Test†; **Neth.**: Allergopharma; Allergovit; Alutard; Artu; Artuvac; Bencard Prikestoplossing; Depot-Hal; Immunovac†; Novo-Helisen; Oraigen; Phargalgen; Pollinex; Purethal; Soluprick SQ; Subilvac B.E.S.T.†; **Norw.**: Alutard; **NZ.**: Albay; Allpyral†; True Test; **Pol.**: Allergovit; Alutard SQ; Alyostal; Catalet; Novo-Helisen; Perosal; Phargalgen; Phostal; Pollinex; Purethal; Staloral; Venomahal; **Port.**: Grazax; Polagen†; Soluprick; Truetest; **S.Afr.**: Albay; Albe; Allpyral Pure Mite; Allpyral Special Grass; EH Retard†; Tol†; **Swed.**: Alutard SQ; Aquagen SQ; Soluprick SQ; **Switz.**: Alvac-S†; ALK; Allergovit; Alutard SQ; Alyostal; ASD†; Novo-Helisen; Phargalgen; Phostal; Polvac; Staloral; **UK.**: Bencard Skin Testing Solutions; Grazax; Phargalgen; Pollinex; **USA.**: Albay; Allpyral; Center-Alt; Phargalgen; True Test; Venomil.

Multi-ingredient. **Arg.**: Summavac; **Braz.**: Allergol; Aminovac; Multi-gen AL†; Multivac VR†; Rhinovac†; Urtivac; Vag Oral; **Cz.**: Apisarthron; Phostal; **Fin.**: Alutard SQ; Aquagen SQ; Soluprick SQ; **Ger.**: Alustal; BU Pangramin SLT†; Depigoid; Forapin E†; Slit One; Subilvac; **Ital.**: Alustal; **Neth.**: Trolab; Venomahal†; **Rus.**: Apisarthron (Апизартрон); **Switz.**: Alustal.

Almond Oil

Aceite de Almendra; Almendras dulces, aceite de; Amande, huile d'; Amygdalae oleum; Badem Yağı; Bitter Almond Oil; Expressed Almond Oil; Huile d'Amande; Mandelöl; Mandelölj; Mandlový olej; Mandulaölaj; Manteliölj; Migdolų aliejus; Ol. Amygdal.; Olej migdalowy; Oleo de Amêndoas; Olio di Mandorla; Sweet Almond Oil.

CAS — 8007-69-0.

Pharmacopoeias. In *USNF*.

Eur (see p.vii) includes the virgin oil and a refined oil.

Fr. also specifies Huile de Noyaux, an oil obtained from various species of *Prunus*.

Ph. Eur. 6.2 (Almond Oil, Virgin; Amygdalae Oleum Virginalae). A yellow, clear, liquid. It is the fatty oil obtained by cold expression from the ripe seeds of *Prunus dulcis* var. *amara* or *P. dulcis* var. *dulcis* or a mixture of both varieties. Slightly soluble in alcohol; miscible with petroleum spirit. Store in well-filled containers. Protect from light.

Ph. Eur. 6.2 (Almond Oil, Refined; Amygdalae Oleum Raffinatum). The fatty oil obtained by refining and deodorisation of Almond Oil. It may contain a suitable antioxidant. A pale yellow, clear, transparent liquid. Slightly soluble in alcohol; miscible

with petroleum spirit. Store in well-filled containers. Protect from light.

USNF 26 (Almond Oil). The refined fixed oil expressed from the kernels of varieties of *Prunus dulcis* [*Prunus amygdalus*] (Rosaceae). It may contain suitable antioxidants. A clear, colourless or pale straw-coloured, oily liquid with a bland taste. Slightly soluble in alcohol; miscible with chloroform, with ether, with petroleum spirit, and with benzene. Store in well-filled, airtight containers. Protect from light.

Profile

Almond oil, which consists mainly of glycerides of oleic acid with smaller amounts of linoleic and palmitic acid, has nutritive and demulcent properties. It is used as an emollient and to soften ear wax. It is also used as a vehicle in some injections.

Preparations

BP 2008: Almond Oil Ear Drops;

USP 31: Rose Water Ointment.

Proprietary Preparations (details are given in Part 3)

Braz.: Laderm; **Mex.**: Dermoskin†.

Multi-ingredient. **Arg.**: Caien; **Austral.**: Curash Babycare; Snor-Away†; **Chile:** Akerat; **Cz.**: Balmador; **Ger.**: Excipial; **Ital.**: Baby Zanzara; Babinster; Otosan Natural Ear Drops†; Proctonet†; Stiomagic†; **Mex.**: Calderm; Liniderm; **NZ:** Am-O-Lin; Snorenz; **Port.**: Cuidaderma; Oidermil; **Spain:** Pasta Lassar Imba; **Switz.**: Antidry; Balmador; Premador; Viola; Wolderma†; **Turk.**: Balmador; Metamorfoz; **UK:** Calendula Napary Change Cream; Earex; Imuderm; Infaderm; Snor-Away.

Alpha Galactosidase A

α-D-Galactosidase; α-Galactosidase A; α-D-Galactoside Galactohydrolase.

Agalsidase Alfa (BAN, USAN, rINN)

Agalsidase alfa; Agalsidasum Alfa.

Агальсидаса Альфа

CAS — 104138-64-9 (protein moiety).

ATC — A16AB03.

ATC Vet — QA16AB03.

Agalsidase Beta (rINN)

Agalsidasum Beta; Agalsidaz Beta; Alfasisada β.

Агальсидаса Бета

CAS — 104138-64-9 (protein moiety).

ATC — A16AB04.

ATC Vet — QA16AB04.

Adverse Effects, Treatment, and Precautions

IgG antibodies to agalsidase alfa develop in some patients, and to agalsidase beta in the majority of patients. The presence of antibodies increases the risk of infusion reactions. Infusion reactions have been reported in about 14% of patients given agalsidase alfa, and in about 67% of patients treated with agalsidase beta. The frequency of the onset of these reactions decreases with continued use, with the majority of reports occurring during the first 2–4 months after the start of treatment, although onset after 1 year has also been reported. Symptoms generally start during, or within 1 hour of, infusion. The most common symptoms have included chills, dyspnoea, facial flushing, headache, nausea, fever, and fatigue. The infusion may be interrupted for about 5 to 10 minutes and restarted once symptoms have subsided. Pre-treatment with oral antihistamines, paracetamol, ibuprofen, and/or corticosteroids 1 to 24 hours before infusion has been used to prevent subsequent reactions. Patients with compromised cardiac function should be monitored closely since they may be predisposed to a higher risk of severe complications arising from infusion reactions.

Interactions

Agalsidase alfa or beta should not be used with amiodarone, chloroquine, monobenzene, or gentamicin, which all have the potential to inhibit intracellular α-galactosidase activity.

Pharmacokinetics

The pharmacokinetic properties of agalsidase alfa appear to be unaffected by dose; the elimination half-life from blood following a single dose has been reported to be about 100 minutes. The pharmacokinetics of agalsidase beta indicate a saturated clearance; the elimination half-life following a single dose has been reported to range from 45 to 100 minutes.

◇ Most pharmacokinetic parameters of agalsidase alfa in children with Fabry disease were similar to those in adult patients after single and repeated doses, except for serum clearance, which was age dependent being significantly increased in children.¹ However, there was no difference in pharmacodynamics between the age groups.

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Uses and Administration

Alpha galactosidase A is an endogenous enzyme that hydrolyses terminal α-D-galactose residues in oligosaccharides and galactolipids into more easily digestible mono- and disaccharides. A form derived from a fungal source is used to prevent intestinal gas.

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 (Gb₃) 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 alfa⁷ and beta.⁸ Results from controlled studies show this form of therapy to be effective in clearing deposits from the kidneys, heart, and skin⁹⁻¹² as well as improving peripheral neuropathy.¹³ An open-label extension study¹⁴ of agalsidase beta in the 58 patients formerly studied in a 20-week controlled phase III study¹¹ 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 therapy¹⁹ 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.

Alpha₁-proteinase Inhibitor

Alpha₁ Antitrypsin; alpha-1-Antitrypsin; Antitrypsin alpha-1; Inhibidor de la α_1 -proteasina.

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 alpha₁-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 alpha₁-proteinase inhibitor is a serum glycoprotein synthesised in the liver that acts as an elastase inhibitor, primarily inhibiting neutrophil elastase. Alpha₁-proteinase inhibitor, prepared from pooled human plasma, is used as replacement therapy in patients with emphysema who have congenital alpha₁ 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 alpha₁-proteinase inhibitor is under investigation for nebulised delivery in congenital alpha₁ antitrypsin deficiency and cystic fibrosis (see below).

Alpha₁-proteinase inhibitor has also been investigated for the prevention of bronchopulmonary dysplasia (p.1500) in preterm neonates.

Alpha₁ antitrypsin deficiency. Alpha₁ antitrypsin deficiency (alpha₁-proteinase inhibitor deficiency) is characterised by chronic obstructive pulmonary disease (COPD) and chronic liver disease associated with a lack of alpha₁-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 alpha₁-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 abnormality⁵ and has been recommended in those patients with some deterioration of lung function.^{2,6} In a short-term study⁷ serum and secretion concentrations of alpha₁-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 alpha₁-proteinase inhibitor to above the protective threshold, and reduction in elastase activity and levels of leukotriene B₄ levels (thought to be important in producing airway inflammation in alpha₁ antitrypsin deficiency). A small placebo-controlled study⁸ found that the rate of decline of FEV₁ was not affected in patients treated for at least 3 years. Data⁹ from a large registry of patients also suggested that, overall, treatment did not affect the rate of decline of FEV₁, but that it decreased mortality, although this may be influenced by other factors. Evaluation⁶ 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 Society¹⁰ recommends that replacement therapy should be reserved for patients with an FEV₁ between 35 and 65% predicted who are no longer smoking and on optimal medical therapy but continuing to show a rapid decline in FEV₁. In a retro-

spective cohort study¹¹ 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 FEV₁ 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 alpha₁-proteinase inhibitor and is managed symptomatically.²

Several new approaches to treatment of alpha₁ antitrypsin deficiency are under investigation:^{2,3,12} plasma-derived and recombinant forms of alpha₁-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. Alpha₁-proteinase inhibitor given by nebuliser is therefore under investigation¹⁻³ in patients with cystic fibrosis (p.166).

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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); Alteenajuri (marshmallow root); Alteenlehti (marshmallow leaf); Altea; 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; Orvosizil-gyökér (marshmallow root); Orvosizilz-level (marshmallow leaf); Proskurníkovy kořen (marshmallow root); Proskurníkovy list (marshmallow leaf); Svilarožň lapai (marshmallow leaf); Svilarožň 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; Althaeae 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.