pathic disease) accounts for 90% or more of cases and occurs especially in Ashkenazi Jews. More than half of all patients with type 1 disease are diagnosed before the age of 10 years.[5] The disease follows a chronic course of variable severity and onset, with hepatosplenomegaly and blood and bone disorders being the main features; there is no neurological involvement. In **type 2 Gaucher disease** (acute infantile neuronopathic disease), neurological involvement predominates. Patients show developmental delay by the age of 6 months, suffer seizures, pulmonary infections, and usually die in early childhood. **Type 3 Gaucher disease** is a subacute neuronopathic form and is slowly progressive.[4] There are 3 subtypes varying in severity and prognosis: in type 3a, there is slow progressive neurological deterioration with death usually occurring during childhood; in type 3b (Norrbotten disease) there is slow cognitive deterioration and patients may survive to adulthood; type 3c typically affects patients of Palestinian, Arab, or Japanese descent, with possible survival to the teenage years.

Treatment of Gaucher disease was previously limited to symptomatic management until the development of enzyme replacement therapy with β-glucocerebrosidase. Due to the rarity of Gaucher disease, early clinical studies were limited mainly to small case series of patients with type 1 disease. Use of alglucerase or imiglucerase has been shown to reverse hepatosplenomegaly and the haematological abnormalities;[6,7] effects may be seen within a few months, although in many the response is poor during the first 6 to 9 months and then improves rapidly.[2] Return to normal haemoglobin values within 6 to 12 months has been reported, as has reduction in liver size by 20 to 30% within 2 years and 30 to 40% by 5 years; a 50% reduction in spleen size also occurred.[8] Bone symptoms respond more slowly. Decreases in bone pain during the first year of treatment have been reported although there was no radiological improvement.[7] Existing bone manifestations are slow to respond or refractory to enzyme replacement therapy, but alendronate has been shown to be of benefit as adjunctive therapy for osteopenia in 36 adults with negative lumbar bone mineral density scores who had been receiving glucocerebrosidase for at least 2 years.[9] Normalised growth velocity has been reported in children[10] and radiographical assessments have shown improvements in bone density and mineralisation.[11] There is evidence that long-term enzyme replacement therapy for up to 5 years completely or partially ameliorates anaemia, thrombocytopenia, organomegaly, and bone pain in patients with type 1 Gaucher disease, as well as preventing further deterioration.[8] However, successful symptom control is dependent on the degree of damage that has already occurred, and early initiation of therapy is recommended for a more favourable prognosis. Enzyme replacement therapy in Gaucher disease is lifelong and relapses occur with prolonged interruptions to therapy.[5,12] Alglucerase has also been tried in rare cases of Gaucher disease affecting the heart[13] or the eye.[14] It is not yet known whether enzyme replacement therapy is able to prevent the development of symptoms in asymptomatic patients.

The efficacy of enzyme replacement therapy in managing neurological symptoms in patients with type 2 or type 3 disease[15] remains to be established. Most of the patients with type 3 Gaucher disease in a small study[16] did not deteriorate neurologically when treated with doses that reversed almost all the systemic manifestations. However, it was pointed out that the amount of enzyme that crosses the blood-brain barrier is unlikely to be significant, and other forms of treatment specifically for neuronopathic Gaucher disease need to be developed.

For those patients with type 1 Gaucher disease in whom enzyme replacement therapy may be unsuitable, miglustat may be used. It reduces the synthesis of glucocerebroside by inhibiting glucosyltransferase, one of the early enzymes in the sphingolipid biosynthetic pathway. However, the balance of benefits versus adverse affects with miglustat is less favourable than with imiglucerase, which remains the standard treatment where possible; the two drugs should not be used together.[17]

Possible future therapies under investigation for Gaucher disease include oral therapy with the pharmacological chaperone isofagomine, and gene therapy. Other modified forms of β-glucocerebrosidase are also under investigation to improve uptake into the affected macrophages.

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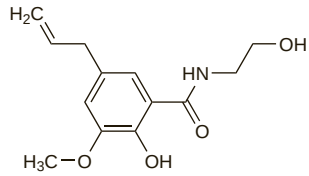
Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Cerezyme; ***Austria:*** Cerezyme; ***Belg.:*** Cerezyme; ***Canad.:*** Cerezyme; ***Cz.:*** Cerezyme; ***Denm.:*** Cerezyme; ***Fin.:*** Cerezyme; ***Ger.:*** Cerezyme; ***Gr.:*** Cerezyme; ***Hong Kong:*** Cerezyme; ***Israel:*** Ceredase†; Cerezyme; ***Ital.:*** Cerezyme; ***Jpn:*** Ceredase†; Cerezyme; ***Neth.:*** Cerezyme; ***Norw.:*** Cerezyme; ***NZ:*** Cerezyme; ***Pol.:*** Cerezyme; ***Port.:*** Cerezyme; ***S.Afr.:*** Cerezyme; ***Spain:*** Cerezyme; ***Swed.:*** Cerezyme; ***Switz.:*** Cerezyme; ***UK:*** Cerezyme; ***USA:*** Ceredase; Cerezyme.

Alibendol *(rINN)*

Alibendolum. 5-Allyl-*N*-(2-hydroxyethyl)-3-methoxysalicylamide.
Алибендол
$C_{13}H_{17}NO_4$ = 251.3.
CAS — 26750-81-2.



Profile

Alibendol is a choleretic used in the treatment of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Cebera†.

Allergen Products

Alergenos; Allergeenivalmisteet; Allergenprodukter; Producta allergenica; Produits allergènes.

Adverse Effects and Treatment

Adverse effects to allergen products can range from mild local reactions to severe generalised reactions that may be fatal, especially reactions to bee and wasp venom. Hypersensitivity reactions may be immediate or delayed.

Adverse effects with **skin-prick testing** are uncommon, although swelling and irritation at the injection site, rhinitis, urticaria, wheezing, and chest tightness might occur, and rarely, anaphylactic shock.

Allergen immunotherapy injections may give rise to swelling, irritation, redness, and hardness at the injection site. Systemic reactions include itching eyes, sneezing, cough, wheezing, chest tightness, atopic eczema, urticaria, and oedema. Anaphylactic shock or severe delayed reactions may also occur. Commonly reported adverse effects with allergen preparations given sublingually include oral oedema, pruritus, and paraesthesia, throat irritation, sneezing, rhinitis, nasal congestion, itching of the eyes and ears, and headache; systemic reactions may occur if the dosage regimen is not adhered to.

Severe reactions to allergen products normally occur within 30 minutes and should be treated promptly with intramuscular adrenaline injection 1 in 1000. Full supportive measures should be implemented and treatment with antihistamines and corticosteroids may be required (for a discussion of the treatment of anaphylaxis and anaphylactic shock, see p.1205). Further allergen immunotherapy should be stopped or continued at reduced dosage depending on the severity of the reaction and in accordance with the licensed product information.

◊ Reviews.

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◊ In 1986 the UK CSM reported[1] that hyposensitising vaccines have the potential to induce severe bronchospasm and anaphylaxis, and that these reactions had caused 26 deaths in the UK since 1957. The majority of patients had no reaction to previous hyposensitising injections. In 1989 the FDA reported that since 1980, the American Academy of Allergy and Immunology and the FDA had received 14 reports of death after allergen immunotherapy, and 4 deaths after skin testing for allergies.[2] The most common clinical factor in these patients was a history of asthma.

In view of these and other reports, recommendations have been made to minimise the risks of systemic reactions.[3-6] Allergen immunotherapy should only be used for seasonal allergic rhinoconjunctivitis not responding to anti-allergic drugs, and for severe hypersensitivity to Hymenoptera stings. In the UK[4] such treatment has usually been avoided in patients with asthma (although asthma is not an absolute contra-indication to Hymenoptera allergen immunotherapy), but elsewhere[3,5,6] asthmatic patients whose asthma is stable and not severe may be treated. Hyposensitising agents should be used only where facilities for full cardiopulmonary resuscitation are immediately available. The recommended length of time after injection that patients should be kept under medical observation varies from 30 minutes[3] to 1 hour.[4] If the patient develops even mild symptoms of a general reaction, observation should be extended until they are completely resolved. The observation period should also be extended for patients at high risk of reactions.

Of 12 samples of *Aspergillus* extract used for allergen immunotherapy, 4 were found to contain aflatoxin (p.2249), one being highly mutagenic as determined by the Ames' test. The results suggested that careful screening of commercially available mould extracts was warranted.[7]

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Precautions

Patients should be observed for at least 30 to 60 minutes after administration of allergen products because of the risk of anaphylaxis (see also under Adverse Effects, above). Patients should avoid taking beta blockers since adrenaline may be ineffective if hypersensitivity reactions occur. Antiallergic medication taken concomitantly may mask the patient's reactivity.

Skin-prick testing should not be carried out in areas where there are skin lesions. Patients should be instructed not to rub or scratch the test site. Antiallergic medication should be stopped before allergen testing to prevent false negative reactions. Systemic or long-term topical use of potent corticosteroids may also mask skin reactivity.

Allergen immunotherapy should not be used in patients with serious immunological illness, cancer, disorders of amino acid metabolism, bleeding disorders, or hyperthyroidism. It should also be avoided during infections or febrile conditions, and administration of an allergen preparation delayed for 24 to 48 hours after recovery. Allergen immunotherapy should be avoided during pregnancy because of the risk to the fetus of any systemic reactions in the mother. Patients with asthma may be more susceptible to hypersensitivity reactions with allergen products and it is considered that allergen immunotherapy should be avoided or used with caution. Injection immunotherapy should be avoided in children under 6 years of age, and sublingual immunotherapy in children under 2 years. Sublingual immunotherapy is contra-indicated in patients with severe oral inflammatory conditions such as lichen planus with ulcerations, or severe mycosis. Sublingual immunotherapy should be stopped for 7 days in patients who have oral surgery, including dental extraction, to allow the wounds to heal.

Allergen immunotherapy should be avoided or used with caution in patients with cardiovascular or pulmonary insufficiency, or severe eczema. Rarely, patients may experience drowsiness with allergen immunotherapy preparations and, if affected, should avoid driving or operating machinery.

Allergen immunotherapy injections should only be given where facilities for full cardiopulmonary resuscitation are immediately available. Injections for immunotherapy should be given subcutaneously and not intravenously or intramuscularly. Patients should avoid strenuous exercise for at least 12 hours after injection immunotherapy, or 1 hour before and after sublingual immunotherapy. It is also recommended to avoid heavy meals and alcohol around the time of injection with some products. Severe anaphylactoid reactions have been reported in patients undergoing allergen immunotherapy who are also receiving ACE inhibitors (see Hypersensitivity, p.1195). Some manufacturers suggest that the reaction could be avoided by temporarily withholding ACE inhibitor therapy during each desensitisation. Allergen immunotherapy preparations and vaccines against infectious diseases should not be given within at least a week of each other or until all possible reactions to either vaccine have disappeared.

Interactions

For precautions to be observed in using allergen products in patients receiving ACE inhibitors, antiallergic drugs, beta blockers, or vaccines see Precautions, above.

Uses and Administration

Allergen products are used diagnostically in skin tests and provocation tests to confirm the cause of a suspected hypersensitivity reaction. They are also used for allergen immunotherapy in certain patients with hypersensitivity reactions, particularly to insect venoms such as bee or wasp venom, pollen (p.2370), house dust, and house-dust mite. Preparations for allergen immunotherapy are given by subcutaneous injection or sublingually. Other routes (such as oral, nasal, or bronchial) have also been tried.

Administration. Allergen vaccines used for allergen immunotherapy (see below) should be well characterised and standardised for total allergenic potency, biological activity, and shelf-life. Whenever possible, the same batch of allergen should be used during a course of treatment because of possible differences in potency between batches. Injections for allergen immunotherapy are given subcutaneously as aqueous extracts or combined with adjuvants to reduce adverse effects while retaining or enhancing immunogenicity. Such modified vaccines are slow-release formulations and therefore the interval between injections is increased. Vaccines can be physically modified by adsorption onto an inert carrier such as aluminium or calcium salts, or tyrosine, or chemically modified with glutaral, formaldehyde, or liposomes. Combinations of the two types of modified vaccine may also be used.

Dosage regimens for allergen immunotherapy are as recommended by the manufacturers and depend on the sensitivity of the patient. During the initial build-up phase, the dose of allergen vaccine is slowly increased (by increasing the concentration and/or the dose volume) until the maintenance dose is reached. However, the dose should be reduced after a systemic reaction, or stopped if the reaction is severe. Likewise, the dose might need to be reduced or not given at all to highly sensitised patients during periods of natural exposure to the allergen.

In *conventional* build-up schedules, injections of aqueous extracts are given once or twice weekly, with maintenance expected to be reached in 4 to 6 months. Depot preparations are given every 1 to 2 weeks. *Modified dosage schedules* have been used where maintenance needs to be achieved more quickly; such regimens may, however, be associated with an increased risk of adverse reactions, although this can be ameliorated by premedication with an antihistamine. Aqueous extracts should be used for modified schedules until the maintenance dose is reached. In *cluster schedules* several injections may be given on the same day, usually at 30-minute intervals, once or twice a week on non-consecutive days. Fewer total injections are used than with conventional schedules and maintenance therapy can be reached in as little as 4 weeks. There might be a slight increase in risk of systemic reactions. *Rush schedules* are more rapid than cluster schedules and several injections are given at specified intervals once daily on consecutive days allowing maintenance doses to be reached in a matter of days; naturally, this does increase the risk of systemic adverse effects and patients need to be monitored more closely and for longer than with conventional schedules. *Ultrarush schedules* are even faster and may be used to accelerate desensitisation to stinging insects in highly sensitive individuals. When the maintenance dose has been reached, the injection interval is progressively increased as necessary according to safety and efficacy. Injection intervals are typically 2 to 4 weeks for aeroallergens and 8 weeks for insect venom. The optimal duration of allergen immunotherapy is unknown, but a period of 3 to 5 years is usually recommended; the decision to discontinue therapy will depend on individual response. Some patients will remain desensitised after stopping allergen immunotherapy but others will relapse.

The sublingual route is also used for allergen immunotherapy, with the vaccine given daily either as a solution or as oral lyophilisate tablets. It is considered to be a good alternative to the subcutaneous route in terms of safety and efficacy, although problems of determining the optimal vaccine dose in relation to efficacy and duration of treatment still remains to be established. The oral, nasal, and bronchial routes have also been tried for allergen immunotherapy, although efficacy or safety has not always been demonstrated.

Modification of allergens is being investigated as an alternative way to increase safety and efficacy, and developments include recombinant proteins, peptides, plasmid DNA vaccines, and immunostimulatory sequences of DNA conjugated to specific allergens. Other immunomodulatory methods include use of allergen-specific antibodies or fragments, and humanised anti-IgE monoclonal antibodies (e.g. omalizumab, p.1128). Also, more efficient adjuvants such as monophosphoryl lipid A are being tried.

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Allergen immunotherapy. Allergic reactions are type I (immediate) hypersensitivity reactions mediated by IgE antibodies (see under Hypersensitivity, p.561) that are usually managed by anti-allergic medication or, where possible, allergen avoidance. For patients in whom these treatment methods are inadequate or unsuitable, allergen immunotherapy (desensitisation or hyposensitisation) may be tried. Specific allergen immunotherapy (SIT) is the administration of gradually increasing quantities of an allergen vaccine to a patient with diagnosed IgE-mediated allergy until a maintenance dose is reached that is effective in ameliorating symptoms associated with subsequent exposure to the allergen.[1-4] The mechanism of action is thought to be through T-helper (Th) cell switching by rectifying the balance between Th1 and Th2 lymphocytes and increasing the levels of protective IgG while decreasing the levels of IgE.[2,4-6] Long-lasting benefit is conferred, and the quality of life improved in patients for whom allergen avoidance is difficult or impossible. Patients must have demonstrable evidence of specific IgE antibodies before undergoing allergen immunotherapy (see Diagnostic Use below), and it is generally recommended that diagnosis of allergies and allergen immunotherapy should only be carried out in specialist centres. Subcutaneous injection immunotherapy (SCIT) is the traditional method of administration and has a long history of use. Sublingual immunotherapy (SLIT) is now also widely used, and other routes have been tried — see Administration, above. Reports of severe and sometimes fatal hypersensitivity reactions to injected allergen preparations prompted recommendations to reduce the risk of systemic reactions (see under Adverse Effects, above).

The use of allergen immunotherapy has been reviewed[4,7] and recommendations have been published.[2,3,8,9] The incidence and severity of allergic disease is increasing as a result of environmental changes, and allergies represent a major cause of illness in developed countries; in the UK for example, they are estimated to affect 1 in 3 people. Of particular concern is the rise in multi-system allergies.[4] Common sources of allergens include: pollen and fungal spores producing seasonal allergic rhinitis and conjunctivitis (hay fever); house dust, house-dust mites, and animal dander producing perennial allergic rhinitis; venom from bees, wasps, and stinging ants; latex rubber, flour, and other allergens giving rise to occupational rhinitis; drugs (e.g. penicillins, anaesthetics); and some foods (e.g. nuts, shellfish).[4] Allergic reactions are a common cause of childhood asthma and are also associated with atopic eczema.[4]

Not all allergies are suitable for treatment with specific allergen immunotherapy and recommendations made by the CSM[10] in the UK are that allergen immunotherapy should only be used for seasonal allergic rhinitis (hay fever) in patients not responsive to anti-allergic drugs, and for hypersensitivity to bee and wasp venoms; warnings against use in patients with asthma are also given (although allergen immunotherapy is used in some countries for the treatment of allergic asthma — see below). The UK CSM[10] also concludes that there is inadequate evidence of benefit from desensitisation to allergens such as house dust, house-dust mites, animal dander, and foods, and therefore does not recommend allergen immunotherapy in these cases.

Allergen immunotherapy is used in **children** and is thought to be more effective than in adults.[2] It has been suggested that its use in children with allergic rhinoconjunctivitis may also prevent the development of asthma.[3] Review of controlled studies and meta-analyses[11] confirmed that allergen injection immunotherapy is effective in allergic asthma in children, and early intervention may prevent progression to multiple allergen hypersensitivity. However, since adverse effects of allergen immunotherapy are more likely in asthmatics, it is contra-indicated in unstable asthma (see also below). Therapy is generally not recommended for children younger than 5 or 6 years of age[2,3,8] because it is less well tolerated, cooperation with a young child might be difficult,[3] and in this age group the differential diagnosis between allergic rhinitis and viral infection of the respiratory tract may not be clear.[2]

Allergen immunotherapy for seasonal **allergic rhinitis** and **conjunctivitis** triggered by pollen has generally been reserved for severely affected patients when anti-allergic drugs have failed.[2,3,8] A systematic review[5] of controlled studies concluded that there is a significant reduction in symptoms and use of medication in suitably selected patients who have not responded adequately to anti-allergic drugs, together with a known and relatively low risk of serious adverse effects with no long-term consequences. The sublingual route is a means of ameliorating the severe systemic reactions associated with injection immunotherapy. A systematic review[6] of studies using sublingual immunotherapy in patients with seasonal and perennial allergic rhinitis supported the promotion of this route because rhinitis symptoms and use of anti-allergic medication were reduced significantly in adults and no systemic adverse effects were reported. However, it was difficult to assess the magnitude of the effect and compare this route with injection immunotherapy. The treatment effect in children was not significant. However, a meta-analysis[12] of more controlled studies involving a greater total number of children concluded that sublingual immunotherapy was effective in children with allergic rhinitis.

There is some evidence that allergen immunotherapy for allergies such as rhinitis may prevent the development of **asthma**[3] and thus earlier use may be warranted.[13] A systematic review[14] of randomised controlled studies confirmed that allergen immunotherapy in asthmatic patients reduced the symptoms of asthma and the use of asthma medication, although it was not possible to quantify the benefits compared with other forms of therapy, and the possibility of severe or fatal anaphylaxis remains. Recommendations for the use of allergen immunotherapy in patients with asthma vary. Guidelines issued in the UK[10] in 1994 recommended that asthmatic patients should not be treated with allergen immunotherapy because they are more likely to develop severe adverse effects (although asthma is not considered a contra-indication to allergen immunotherapy for anaphylaxis caused by Hymenoptera spp.). Others,[3,9] including WHO,[2] consider that allergen immunotherapy for allergic rhinoconjunctivitis can be given to patients whose asthma is stable and not severe (FEV_1 is not less than 70% of predicted value),[2] when avoidance of allergens has not been sufficient or is not possible, and drug treatment has failed. Allergen immunotherapy should not be given to patients whose asthma can be controlled by antiasthmatic drugs and allergen avoidance.[15]

Allergen immunotherapy is indicated for patients with specific IgE antibodies who have experienced severe anaphylaxis after **insect stings**, particularly those of Hymenoptera (bees, wasps, and stinging ants).[2,3,8,16,17] Vaccines containing purified venom are available for most Hymenoptera spp. and have replaced whole body extract preparations, which were generally found to be ineffective. Venom immunotherapy is very effective in decreasing the risk of systemic reactions to venom in susceptible people.[17] Venom vaccines are not available for stinging ants but whole body extract vaccines may contain sufficient venom antigens to be effective.[2,3,17] Allergen immunotherapy for rhinoconjunctivitis and asthma due to house-dust mite or animal dander can be considered when the allergen is unavoidable.[2,3,9,14] A review[18] considering both injection and sublingual mite immunotherapy in adults and children with asthma and/or rhinitis confirms efficacy, although it is not possible to assess safety relative to other forms of allergen immunotherapy such as pollen vaccines. One multicentre, randomised, dose-response study[19] found that specific mite injection immunotherapy for 1 year improved eczema in patients with atopic dermatitis allergic to house-dust mite. Limited data indicate that allergen immunotherapy might be effective for atopic dermatitis associated with aeroallergen sensitivity.[3] However, more controlled studies are needed to confirm its place in treatment.[4]

Allergen immunotherapy for **drug hypersensitivity** may be warranted on the rare occasions when continued use is considered essential, possibly with penicillins or insulin.[8,20] In most cases the effect of desensitisation is temporary and if the medication is required again in the future, the process must be repeated.[21]

Allergen immunotherapy has also been tried in **other disorders** such as urticaria and food allergies, but there is insufficient evidence to support such use[3,4,8,10] and its use is not recommended. The traditional method of allergen immunotherapy in peanut allergy has an unacceptably high rate of systemic adverse reactions and other immunotherapeutic interventions are being sought.[22]

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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; Pharmalgen; Pollinex†; ***Braz.:*** Nikkho Vac; ***Canad.:*** Pollinex-R; ***Cz.:*** Alutard SQ; Alyostal; APSI/AQ†; ASAD†; D-Al; Grazax; H-AL; Pangramin; Pollinex; Soluprick SQ; Staloral; ***Denm.:*** Alutard SQ; Aquagen SQ; Pharmalgen; Sensitiner; Soluprick SQ; True Test; ***Fr.:*** Albey; Alyostal; ASAD†; Diallertest; ***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; Venomenhal; Venomil; ***Hung.:*** Lais; Pangramin; Purethal; Venomenhal; ***Israel:*** True Test; ***Ital.:*** Phostal; Staloral; ***Mex.:*** True Test†; ***Neth.:*** Allergopharma; Allergovit; Alutard; Artu; Artuvac; Bencard Priktestoplossing; Depot-Hal; Immunovac†; Novo-Helisen; Oralgen; Pharmalgen; Pollinex; Purethal; Soluprick SQ; Sublivac B.E.S.T.†; ***Norw.:*** Alutard; ***NZ:*** Albay; Allpyral†; True Test; ***Pol.:*** Allergovit; Alutard SQ; Alyostal; Catalet; Novo-Helisen; Perosall; Pharmalgen; Phostal; Pollinex; Purethal; Staloral; Venomenhal; ***Port.:*** Grazax; Polagen†; Soluprick; Truetest; ***S.Afr.:*** Albay; Albey; Allpyral Pure Mite; Allpyral Special Grass; EH Retard†; Tol†; ***Swed.:*** Alutard SQ; Aquagen SQ; Soluprick SQ; ***Switz.:*** Alavac-S†; ALK; Allergovit; Alutard SQ; Alyostal; ASAD†; Novo-Helisen; Pharmalgen; Phostal; Polvac; Staloral; ***UK:*** Bencard Skin Testing Solutions; Grazax; Pharmalgen; Pollinex; ***USA:*** Albay; Allpyral; Center-Al; Pharmalgen; True Test; Venomil.

Multi-ingredient: ***Arg.:*** Summavac; ***Braz.:*** Alergoral; Aminovac; Multigen AL†; Multivac VR†; Rhinovac†; Urtivac Vag Oral; ***Cz.:*** Apisarthron; Phostal; ***Fin.:*** Alutard SQ; Aquagen SQ; Soluprick SQ; ***Ger.:*** Alustal; BU Pangramin SLIT; Depigoid; Forapin E†; Slit One; Sublivac; ***Ital.:*** Alustal; ***Neth.:*** Trolab; Venomhal†; ***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; Mandelolja; Mandlový olej; Mandulaolaj; Manteliöljy; Migdolų aliejus; Ol. Amygdal.; Olej migdałowy; 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 Virginale). 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 antoxidant. 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 antoxidants. 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.:*** Balmandol; ***Ger.:*** Excipial; ***Ital.:*** Baby Zanzara; Babysteril; Otosan Natural Ear Drops†; Proctonet†; Stilomagic†; ***Mex.:*** Caliderm; Liniderm; ***NZ:*** Am-O-Lin; Snorenz; ***Port.:*** Cuidaderma; Olidermil; ***Spain:*** Pasta Lassar Imba; ***Switz.:*** Antidry; Balmandol; Premandol; Viola; Woloderma†; ***Turk.:*** Balmandol; Metamorfoz; ***UK:*** Calendula Nappy 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)*

Agalsidasa alfa; Agalsidasum Alfa.

Агальсидаза Альфа

CAS — 104138-64-9 (protein moiety).
ATC — A16AB03.
ATC Vet — QA16AB03.

Agalsidase Beta *(rINN)*

Agalsidasum Beta; Agalsidaz Beta; Alfasidasa β.

Агальсидаза 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. Pretreatment 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, monobenzone, 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.

1. Ries M, *et al.* Enzyme replacement in Fabry disease: pharmacokinetics and pharmacodynamics of agalsidase alfa in children and adolescents. *J Clin Pharmacol* 2007; **47:** 1222–30.

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.