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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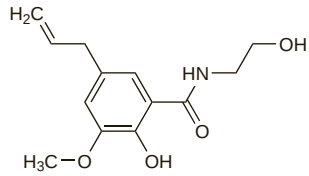
### Preparations

**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.