Aflatoxins

Aflatoxinas.

CAS — 1162-65-8 (aflatoxin B_1); 7220-81-7 (aflatoxin B_2); 1165-39-5 (aflatoxin G_1); 7241-98-7 (aflatoxin G_2); 6795-23-9 (aflatoxin M_1); 6885-57-0 (aflatoxin M_2).

Profile

Aflatoxins are toxic metabolites produced by many strains of *Aspergillus flavus* and *A. parasiticus*, growing on many vegetable foods, notably maize and peanuts. A number of forms, including aflatoxins B_1, B_2, G_1, and G_2 have been identified. Aflatoxins M_1 and M_2 are metabolites produced by animals after ingestion of aflatoxins B_1 and B_2; they may be detected in cows' milk.

Aflatoxins can cause hepatitis and cirrhosis. They have been implicated in liver cancer, and may act as co-carcinogens with hepatitis B virus. Aflatoxin B_1 is reported to be one of the most potent carcinogens known in *animals*. It has been reported that aflatoxins have been developed in some countries as biological weapons.

◊ References.

1. Ross RK, *et al.* Urinary aflatoxin biomarkers and risk of hepatocellular carcinoma. *Lancet* 1992; **339:** 943–6.
2. Jackson PE, Groopman JD. Aflatoxin and liver cancer. *Baillieres Best Pract Res Clin Gastroenterol* 1999; **13:** 545–55.
3. Peraica M, *et al.* Toxic effects of mycotoxins in humans. *Bull WHO* 1999; **77:** 754–66.
4. Pitt JI. Toxigenic fungi and mycotoxins. *Br Med Bull* 2000; **56:** 184–92.

Agnus Castus

Agni Casti; Agni casti fructus; Agnocasto; Chaste Tree Fruit; Chasteberry; Drmkový plod; Gattilier, fruit de; Keuschlamm; Mönchspfeffer; Monk's Pepper; Munkpeppar; Owoc niepokalanka zwyczajnego; Sauzgatillo; Siveydenpuunhedelmä; Zerolo.

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

Ph. Eur. 6.2 (Agnus Castus Fruit). The whole, ripe, dried fruit of *Vitex agnus castus*. It contains a minimum 0.08% of casticin calculated with reference to the dried drug. Protect from light.

USP 31 (Chaste Tree). The dried ripe fruits of *Vitex agnus-castus* (Verbenaceae). It contains not less than 0.05% of agnuside and not less than 0.08% of casticin, calculated on the dried basis.

Profile

Agnus castus is reported to affect the secretion of luteinising hormone, follicle stimulating hormone, and prolactin by the pituitary. Both inhibition and stimulation of prolactin secretion have been reported, and may be dose-dependent. Agnus castus is included in herbal preparations for the symptoms of premenstrual syndrome, including mastalgia; it has also been used for menstrual cycle irregularities or menopausal disorders, but should be avoided in patients receiving exogenous sex hormones, including oral contraceptives.

Homoeopathy. Agnus castus has been used in homoeopathic medicines under the following names: Vitex agnus-castus; Agn. cast.

◊ References.

1. Houghton P. Agnus castus. *Pharm J* 1994; **253:** 720–1.
2. Christie S, Walker AF. Vitex agnus-castus L.: (1) a review of its traditional and modern therapeutic use; (2) current use from a survey of practitioners. *Eur J Herbal Med* 1997; **3:** 29–45.
3. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001; **322:** 134–7.
4. Chrubasik S, Roufogalis BD. Chaste tree fruit for female disorders. *Aust J Pharm* 2001; **82:** 156–7.

Adverse effects, precautions, and interactions. The adverse effects of agnus castus are reported to be mild and reversible, with acne, erythematous rash, headache, gastrointestinal disorders, menstrual disorders, nausea, and pruritus being the most frequently reported. Toxicity data for use of agnus castus during pregnancy and breast feeding are sparse, but in view of its pharmacological actions, use is not recommended. There is a theoretical possibility of drug interactions between agnus castus and dopamine antagonists.[1]

1. Daniele C, *et al.* Vitex agnus castus: a systematic review of adverse events. *Drug Safety* 2005; **28:** 319–32.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Premular; ***Austria:*** Agnofem; Agnucaston; Agnumens; ***Braz.:*** Lutene; Nalle; Regulatum†; Tenag; Vitenon; Vitex; ***Cz.:*** Agnucaston; Evana†; ***Ger.:*** Agno-Sabona†; Agnolyt; Agnucaston; Agnufemil†; Biofem; Castufemin; Cefanorm; Femicur N; Feminon A; Femisana mens; Gynocastus; Hevertogyn; Kytta-Femin†; Sarai; Strotan; Valverde Monchspfeffer bei Menstruationsbeschwerden†; ***Hung.:*** Agnucaston; Cefanorm; PreMens; ***Indon.:*** Agnu Gyne; Agnucaston; ***Mex.:*** Cicloplant; ***Philipp.:*** Ascof; ***Pol.:*** Agufem; Castagnus; ***Rus.:*** Agnucaston (Агнукастон)†; Cyclodynon (Циклодинон); ***Spain:*** Dismegyn; Femiplante; ***Switz.:*** Agnolyt; Emoton; Oprane; Prefemine; PreMens; ***Thai.:*** Agnucaston†; ***Turk.:*** Agnucaston; Biofem; ***UK:*** Herbal Premens; Premherb.

Multi-ingredient: ***Austral.:*** Dong Quai Complex; Feminine Herbal Complex; Lifesystem Herbal Formula 4 Women's Formula†; PMT Complex†; Women's Formula Herbal Formula 3†; ***Canad.:*** Natural HRT; ***Ger.:*** Femisana†; ***Hong Kong:*** Phytoestrin†; ***Indon.:*** Herbalacta; ***Singapore:*** Phytoestrin.

Agrimony

Agrimonia; Agrimoniae herba; Aigremoine; Dirvuolių žolė; Maarianverijuuri; Odermennigkraut; Párlófű; Řepíková nať; Småborre.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Agrimony). The dried flowering tops of *Agrimonia eupatoria* containing a minimum of 2.0% of tannins expressed as pyrogallol, calculated with reference to the dried drug.

Profile

Agrimony, the aerial parts of *Agrimonia eupatoria* (Rosaceae) or more rarely *A. procera* (*A. odorata*; fragrant agrimony), has astringent and diuretic properties. It is used internally for diarrhoea, biliary and other gastrointestinal disorders, and urinary-tract disorders; it has also been used for inflammatory mouth and throat disorders. It has been used externally for wound healing and skin disorders.

Homoeopathy. Agrimony has been used in homoeopathic medicines.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Nat Repiku Lekarskeho†; Repik Lekarsky†; Repikovy Caj, Repikova Nat†.

Multi-ingredient: ***Austria:*** Amersan; Gallen- und Lebertee St Severin; Novocholin; ***Cz.:*** Amersan; Cynarosan†; Eugastrin†; Hemoral†; Naturland Grosser Swedenbitter†; Nontusyl†; Species Cholagogae Planta; Stomaran; The Salvat; Ungolen†; Zlucnikova Cajova Smes; ***Fr.:*** Tisane Hepatique de Hoerdt; ***Ger.:*** Rhoival†; Stomasal Med†; ***Rus.:*** Herbion Drops for the Gallbladder (Гербион Капли Желчегонные); ***Spain:*** Natusor Astringel†; Natusor Farinol†; ***UK:*** Piletabs.

Alfalfa

Lucerne; Purple medick.

Profile

Alfalfa is the plant *Medicago sativa* (Leguminosae) which is cultivated as an animal feedstuff. The seeds and sprouts of alfalfa contain canavanine (2-amino-4-(guanidinooxy)butyric acid), a toxic amino acid structurally related to arginine; content is reported to represent about 1.5% of the dry weight. A syndrome resembling SLE has been recorded in *monkeys* fed alfalfa.

Alfalfa is used in herbal preparations for a variety of disorders.

Homoeopathy. Alfalfa has been used in homoeopathic medicines under the following names: Alfa.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austral.:*** Irontona; Neo-Cleanse; Panax Complex†; Plantiodine Plus†; Vitatona; ***Chile:*** Calcio 520; Fucus Compuesto†; ***Fr.:*** Gonaxine; Gynosoja; Menoxine.

Alfaprostol *(BAN, USAN, rINN)*

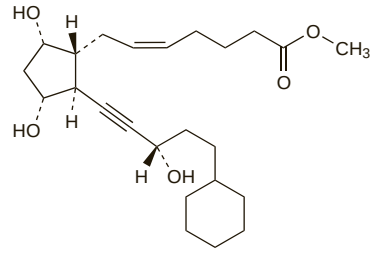
Alfaprostolum; K-11941; Ro-22-9000. Methyl (*Z*)-7-{(1*R*,2*S*,-3*R*,5*S*)-2-[(3*S*)-5-cyclohexyl-3-hydroxypent-1-ynyl]-3,5-dihydroxycyclopentyl}hept-5-enoate.

Альфапростол

$C_{24}H_{38}O_5$ = 406.6.

CAS — 74176-31-1.

ATC Vet — QG02AD94.



Profile

Alfaprostol is a synthetic analogue of dinoprost (prostaglandin F_2). It is used as a luteolytic in veterinary medicine.

Alglucerase *(BAN, USAN, rINN)*

Alglucerasa; Alglucérase; Alglucerasum; Glucosylceramidase; Macrophage-targeted β-Glucocerebrosidase.

Альглюцераза

CAS — 143003-46-7.

ATC — A16AB01.

ATC Vet — QA16AB01.

Description. Alglucerase is a modified form of human placental β-glucocerebrosidase (ceramide glucosidase; β-D-glucosyl-*N*-acylsphingosine glucohydrolase). It is a monomeric glycoprotein of 497 amino acids with glycosylation making up about 6% of the molecule.

Imiglucerase *(BAN, USAN, rINN)*

Imiglucerasa; Imiglucérase; Imiglucerasum; Imiglukeraasi; Imiglukeras; Imigluseraz; Recombinant Macrophage-targeted β-Glucocerebrosidase; r-GCR.

Имиглюцераза

CAS — 154248-97-2.

ATC — A16AB02.

ATC Vet — QA16AB02.

Description. Imiglucerase is a recombinant human-derived β-glucocerebrosidase. It is a monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites

Adverse Effects and Precautions

Fever, chills, pruritus, flushing, and gastrointestinal symptoms, including cramps, diarrhoea, nausea, and vomiting have been reported after use of alglucerase or imiglucerase. Some of these may be hypersensitivity reactions; other hypersensitivity reactions, including urticaria and angioedema, respiratory symptoms, and hypotension have also occurred. Anaphylactoid reactions have occurred rarely with imiglucerase. Caution is required in patients who have exhibited signs of hypersensitivity; reduction of the rate of infusion, and pretreatment with antihistamines and/or corticosteroids may permit further treatment. Antibodies have developed in about 15% of patients receiving a glucocerebrosidase enzyme during the first year of therapy. Patients who develop antibodies are at increased risk of hypersensitivity reactions and periodic assessment for antibody formation is recommended.

Pain and irritation at the injection site may occur. Other adverse effects reported include fatigue, dizziness, headache, backache, peripheral oedema, mouth ulcers, and disturbances in sense of smell.

Alglucerase is prepared from human placentas and its infusion therefore carries a risk of transmission of infections although this is minimised by the manufacturing process. Chorionic gonadotrophin, a naturally occurring hormone in human placentas, has been detected in alglucerase. The presence of this hormone may produce early virilisation in young boys if sufficient is given, and has the potential to produce false positive results in pregnancy tests that rely on the detection of this hormone. Alglucerase should be used with caution, if at all, in patients with androgen-sensitive malignancies.

◊ References.

1. Starzyk K, *et al.* The long-term international safety experience of imiglucerase therapy for Gaucher disease. *Mol Genet Metab* 2007; **90:** 157–63.

Effects on the lungs. Pulmonary hypertension developed in 2 patients with Gaucher disease after starting treatment with alglucerase.[1] Neither patient had evidence of parenchymal lung infiltration with Gaucher cells.

1. Dawson A, *et al.* Pulmonary hypertension developing after alglucerase therapy in two patients with type 1 Gaucher disease complicated by the hepatopulmonary syndrome. *Ann Intern Med* 1996; **125:** 901–4.

Pharmacokinetics

After intravenous infusion, plasma enzymatic activities of alglucerase and imiglucerase decline rapidly from steady state, with an elimination half-life of between 3.6 and 10.4 minutes.

Uses and Administration

The enzyme β-glucocerebrosidase is given as imiglucerase (or occasionally alglucerase) for long-term enzyme replacement therapy to patients with symptomatic Gaucher disease (see below). The oligosaccharide chains of the enzyme are modified to terminate with mannose residues to ensure uptake into macrophages.

Imiglucerase is given by intravenous infusion over 1 to 2 hours for the treatment of type 1 or type 3 Gaucher disease. Alternatively, the dose may be infused at a rate not exceeding 1 unit/kg per minute. The dosage depends on the severity of symptoms, and initial doses can vary from 2.5 units/kg three times weekly to 60 units/kg once every two weeks. Further increases or decreases in doses are made according to individual response. Once the patient's condition is stabilised, monitoring and dosage adjustment up or down is carried out at usual intervals of 6 to 12 months. In the UK, the *BNFC* notes that higher doses of 120 units/kg infused over 1 to 2 hours are given once every 2 weeks for type 3 Gaucher disease.

Alglucerase has been given by intravenous infusion in similar doses with monitoring and dosage adjustment at intervals of 3 to 6 months in stabilised patients with type 1 Gaucher disease.

Gaucher disease. Gaucher disease[1-4] (glucocerebrosidosis) is a rare, autosomal recessive disorder, although it is the commonest lysosomal storage disorder. It is caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase (acid β-glucosidase, ceramide glucosidase, β-D-glucosyl-*N*-acylsphingosine glucohydrolase, or glucosylceramidase) which catalyses the hydrolysis of glucocerebroside, a lipid component of cell membranes, to glucose and ceramide. Deficiency of β-glucocerebrosidase results in accumulation of glucocerebroside in the lysosomes of reticuloendothelial cells, particularly macrophages.

Gaucher disease is **classified** into three main forms based on clinical signs and symptoms. Hepatosplenomegaly occurs in all forms. **Type 1 Gaucher disease** (chronic adult non-neurono-

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.

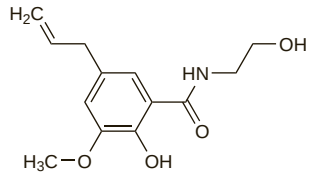
1. NIH Technology Assessment Panel on Gaucher Disease. Gaucher disease: current issues in diagnosis and treatment. *JAMA* 1996; **275:** 548–53.
2. Morales LE. Gaucher's disease: a review. *Ann Pharmacother* 1996; **30:** 381–8.
3. Elstein D, *et al.* Gaucher's disease. *Lancet* 2001; **358:** 324–7.
4. Grabowski GA. Gaucher disease: lessons from a decade of therapy. *J Pediatr* 2004; **144** (suppl): S15–S19.
5. Charrow J, *et al.* Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. *J Pediatr* 2004; **144:** 112–20.
6. Grabowski GA, *et al.* Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. *Ann Intern Med* 1995; **122:** 33–9.
7. Pastores GM, *et al.* Enzyme therapy in Gaucher disease type 1: dosage efficacy and adverse effects in 33 patients treated for 6 to 24 months. *Blood* 1993; **82:** 408–16.
8. Weinreb NJ, *et al.* Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; **113:** 112–19.
9. Wenstrup RJ, *et al.* Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. *Blood* 2004; **104:** 1253–7.
10. Kaplan P, *et al.* Acceleration of retarded growth in children with Gaucher disease after treatment with alglucerase. *J Pediatr* 1996; **129:** 149–53.
11. Rosenthal DI, *et al.* Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase. *Pediatrics* 1995; **96:** 629–37.
12. Drelichman G, *et al.* Clinical consequences of interrupting enzyme replacement therapy in children with type 1 Gaucher disease. *J Pediatr* 2007; **151:** 197–201.
13. Spada M, *et al.* Cardiac response to enzyme-replacement therapy in Gaucher's disease. *N Engl J Med* 1998; **339:** 1165–6.
14. vom Dahl S, *et al.* Loss of vision in Gaucher's disease and its reversal by enzyme-replacement therapy. *N Engl J Med* 1998; **338:** 1471–2.
15. Bembi B, *et al.* Enzyme replacement treatment in type 1 and type 3 Gaucher's disease. *Lancet* 1994; **344:** 1679–82.
16. Altarescu G, *et al.* The efficacy of enzyme replacement therapy in patients with chronic neuronopathic Gaucher's disease. *J Pediatr* 2001; **138:** 539–47.
17. Weinreb NJ, *et al.* Guidance on the use of miglustat for treating patients with type 1 Gaucher disease. *Am J Hematol* 2005; **80:** 223–9.

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.

1. Lockey RF, *et al.* Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol* 2001; **87** (suppl 1): 47–55.
2. Borchers AT, *et al.* Fatalities following allergen immunotherapy. *Clin Rev Allergy Immunol* 2004; **27:** 147–58.
3. Amin HS, *et al.* Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006; **117:** 169–75.

◊ 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]

1. Committee on Safety of Medicines. Desensitising vaccines. *BMJ* 1986; **293:** 948.
2. FDA. Fatality risk with allergenic extract use. *JAMA* 1989; **261:** 3368.
3. Malling H-J, Weeke B, eds. Position paper: Immunotherapy. (EAACI) The European Academy of Allergology and Clinical Immunology. *Allergy* 1993; **48** (suppl 14): 9–35.
4. Committee on Safety of Medicines/Medicines Control Agency. Desensitising vaccines: new advice. *Current Problems* 1994; **20:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 09/05/08)
5. Bousquet J, *et al.* WHO Position Paper: Allergen immunotherapy: therapeutic vaccines for allergic diseases. *J Allergy Clin Immunol* 1998; **102:** 558–62.
6. Joint Task Force on Practice Parameters: American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol* 2007; **120** (3 suppl): S25–S85. Also available at: http://www.jcaai.org/file_depot/0-10000000/20000-30000/27387/folder/63948/IT_supplement.pdf (accessed 28/04/08)
7. Legator MS, *et al.* Aflatoxin B in mould extracts used for desensitisation. *Lancet* 1983; **ii:** 915.

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.