Hypersensitivity. References to asthma developing after occupational exposure to amylases used in the flour milling[1-3] and detergent[4,5] manufacturing industries, and studies[6-8] to assess the likelihood of developing amylase hypersensitivity after ingesting wheat products including bread.

1. Smith TA, *et al.* Respiratory symptoms and wheat flour exposure: a study of flour millers. *Occup Med (Lond)* 2000; **50:** 25–9.
2. Cullinan P, *et al.* Allergen and dust exposure as determinants of work-related symptoms and sensitization in a cohort of flour-exposed workers; a case-control analysis. *Ann Occup Hyg* 2001; **45:** 97–103.
3. Quirce S, *et al.* Glucoamylase: another fungal enzyme associated with baker's asthma. *Ann Allergy Asthma Immunol* 2002; **89:** 197–202.
4. Hole AM, *et al.* Occupational asthma caused by bacillary amylase used in the detergent industry. *Occup Environ Med* 2000; **57:** 840–2.
5. Cullinan P, *et al.* An outbreak of asthma in a modern detergent factory. *Lancet* 2000; **356:** 1899–1900.
6. Cullinan P, *et al.* Clinical responses to ingested fungal alpha-amylase and hemicellulase in persons sensitized to Aspergillus fumigatus? *Allergy* 1997; **52:** 346–9.
7. Sander I, *et al.* Is fungal alpha-amylase in bread an allergen? *Clin Exp Allergy* 2000; **30:** 560–5.
8. Simonato B, *et al.* IgE binding to soluble and insoluble wheat flour proteins in atopic and non-atopic patients suffering from gastrointestinal symptoms after wheat ingestion. *Clin Exp Allergy* 2001; **31:** 1771–8.

Uses and Administration

The term amylase refers to an enzyme catalysing the hydrolysis of α-1,4-glucosidic linkages of polysaccharides such as starch, glycogen, or their degradation products. Amylases may be classified according to the manner in which the glucosidic bond is attacked. Endoamylases attack the α-1,4-glucosidic linkage at random. Alpha-amylases are the only types of endoamylases known and yield dextrins, oligosaccharides, and monosaccharides. The more common alpha-amylases include those isolated from human saliva, mammalian pancreas, *Bacillus subtilis, Aspergillus oryzae*, and barley malt. Exoamylases attack the α-1,4-glucosidic linkage only from the non-reducing outer polysaccharide chain ends. They include beta-amylases and glucoamylases (amyloglucosidases or gamma-amylases) and are of vegetable or microbial origin. Beta-amylases yield beta-limit dextrins and maltose, and glucoamylases yield glucose.

Amylase is used in the production of predigested starchy foods and for the conversion of starch to fermentable sugars in the baking, brewing, and fermentation industries.

Amylase from various sources has been used as an ingredient of preparations of mixed digestive enzymes, and has been given by mouth for its supposed activity in reducing respiratory-tract inflammation and local swelling and oedema. Pancreatic enzymes such as pancreatin (p.2360) and pancrelipase (p.2360) have amylase activity.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Orenzym; ***Fr.:*** Flaviastase; Maxilase; Megamylase; Ribamylase; ***Port.:*** Maxilase.

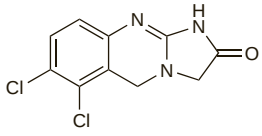
Multi-ingredient: ***Arg.:*** Docechol; Dom-Polienzim; Gastridin-E; Homocisteon Compuesto; Pakinase; Polienzim; Tridigestivo Soubeiran; ***Austral.:*** Enzyme; ***Austria:*** Wobenzym; ***Belg.:*** Digestomen; ***Braz.:*** Bromelin†; Enziprid†; Essen; Filogaster†; Pantopept†; Primeral; Thiomucase; ***Canad.:*** Digesta; ***Chile:*** Flapex E; ***Cz.:*** Wobenzym; ***Ger.:*** Enzym-Wied†; ***Hong Kong:*** Digezym; Enzyplex; Magesto; ***India:*** Aristozyme; Bestozyme; Catazyme-P; Digeplex; Digeplex-T; Dipep; Farizym; Lupizyme; Molzyme†; Neopeptine; Nutrozyme; Papytazyme; Sanzyme-DS; Unienzyme; Vitazyme; ***Indon.:*** Aludonna; Enzyplex; Excelase-E; Librozym; Librozym Plus; Vitazym; Xepazym; ***Ital.:*** Digestopan†; Essen Enzimatico†; ***Jpn:*** Cabagin; ***Malaysia:*** Biotase; Enzyplex; Pepfiz; ***Mex.:*** Ochozim; Wobenzym; Zimotris; ***Port.:*** Modulanzime; ***Rus.:*** Pepfiz (Пепфиз); Wobenzym (Вобэнзим); ***Singapore:*** Biotase; Enzyplex; Weisen-U†; ***Spain:*** Demusin; Digestomen Complex; Paidozim; ***Switz.:*** Zymoplex†; ***Thai.:*** Diasgest; Digestin; Endogest†; Enzyplex; Flatulence; Magesto; Mesto-Of; Papytazyme†; Pepfiz; Pepsitase; Polyenzyme-I; ***UK:*** Enzyme Digest; Enzyme Plus; ***USA:*** Enzyme; Ku-Zyme; Kutrase; Papaya Enzyme; ***Venez.:*** Festal Reformulado.

Anagrelide Hydrochloride *(BANM, USAN, rINNM)*

Anagrélide, Chlorhydrate d'; Anagrelidi Hydrochloridum; BL-4162a; BMY-26538-01; Hidrocloruro de anagrelida. 6,7-Dichloro-1,5-dihydroimidazo[2,1-*b*]quinazolin-2(3*H*)-one hydrochloride.

Анагрелида Гидрохлорид

$C_{10}H_7Cl_2N_3O,HCl$ = 292.5.
CAS — 68475-42-3 (anagrelide); 58579-51-4 (anagrelide hydrochloride).
ATC — L01XX35.
ATC Vet — QL01XX35.



(anagrelide)

Adverse Effects

Adverse effects most commonly reported with anagrelide include headache, palpitations and tachycardia, fluid retention, diarrhoea, nausea, and abdominal pain; fatigue, dizziness, flatulence, vomiting, dyspnoea, skin rash, and anaemia have also occurred. Cardiovascular effects also include vasodilatation and positive inotropic effects; myocardial infarction, cardiomyopathy and heart failure have been reported. Anagrelide has been shown to be embryotoxic and fetotoxic in *animal* studies.

Effects on the heart. High-output heart failure occurred in a patient given anagrelide for essential thrombocytosis.[1] Clinical and haemodynamic adverse effects resolved almost immediately on stopping anagrelide.

1. Engel PJ, *et al.* High-output heart failure associated with anagrelide therapy for essential thrombocytosis. *Ann Intern Med* 2005; **143:** 311–13.

Effects on the lungs. Severe life-threatening hypersensitivity pneumonitis has been associated with anagrelide.[1]

1. Raghavan M, *et al.* Severe hypersensitivity pneumonitis associated with anagrelide. *Ann Pharmacother* 2003; **37:** 1228–31.

Erectile dysfunction. Erectile dysfunction associated with anagrelide therapy has been reported in a patient.[1]

1. Braester A, Laver B. Anagrelide-induced erectile dysfunction. *Ann Pharmacother* 2002; **36:** 1291.

Precautions

Anagrelide is mainly removed from the body by hepatic metabolism, and its use is contra-indicated in patients with severe hepatic impairment. In the UK it is additionally contra-indicated in those with moderate impairment, but in the USA its use is permitted in such patients at reduced doses (see below). Licensed drug information in the UK also contra-indicates its use in those with moderate to severe renal impairment (creatinine clearance less than 50 mL/minute).

Anagrelide should be used with caution in patients with cardiovascular disease. Cardiac function should be assessed in patients before and during treatment, and patients monitored for cardiovascular adverse effects during treatment. For precautions in patients taking anagrelide with aspirin, see Interactions, below.

Platelet counts should be monitored closely, especially at the start of treatment (see Uses and Administration, below). Haemoglobin, white blood cells, and hepatic and renal function should also be monitored until a maintenance dose is established.

Dizziness may affect the performance of skilled tasks such as driving.

Anagrelide should not be used during pregnancy.

Interactions

There is the theoretical possibility that inhibitors of the cytochrome P450 isoenzyme CYP1A2, including grapefruit juice, could reduce the clearance of anagrelide. Anagrelide itself demonstrates limited inhibitory activity towards CYP1A2. Anagrelide may exacerbate the effects of other phosphodiesterase inhibitors such as amrinone, cilostazol, enoximone, milrinone, and olprinone that also produce positive inotropic effects.

Potentiation of the effects of other drugs that modify platelet function when given with anagrelide is a theoretical possibility; although no clinically significant effects have been seen when given with aspirin, the UK manufacturer suggests that the risk-benefit potential should be assessed before using both drugs in patients with a platelet count above 1 500 000 cells/mm^3 and/or a history of haemorrhage.

Pharmacokinetics

Anagrelide is well absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 1 hour after an oral dose on an empty stomach, increasing to 3 hours in the presence of food, although this appears to have no clinically significant effect on bioavailability. It is extensively metabolised, primarily by the cytochrome P450 isoenzyme CYP1A2, and eliminated in the urine; less than 1% of a dose is excreted unchanged. The plasma half-life is about 1.3 hours.

Uses and Administration

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III that reduces platelet production and, at higher than therapeutic doses, inhibits platelet aggregation. It is used to treat primary (essential) thrombocythaemia (p.654) in patients intolerant of, or unresponsive to, other therapy, and also in thrombocythaemia secondary to other myeloproliferative disorders.

Anagrelide is given orally as the hydrochloride monohydrate ($C_{10}H_7Cl_2N_3O,HCl,H_2O$ = 310.6) but doses are expressed in terms of the base; 1.2 mg of anagrelide hydrochloride monohydrate is equivalent to about 1 mg of anagrelide. The initial dose is the equivalent of anagrelide 1 mg daily in 2 divided doses. After at least a week, the dose is adjusted, by increasing the daily dose by not more than 500 micrograms in any one week, until the platelet count is maintained within the normal range. The usual maintenance dose is 1 to 3 mg daily. The dose should not exceed 10 mg daily or 2.5 mg as a single dose. In the USA, a higher initial dose of 2 mg daily, divided into 2 or 4 doses, is used; an initial daily dose of 500 micrograms is recommended in children. For doses to be used in patients with hepatic impairment, see below.

The effects of anagrelide therapy must be regularly monitored: platelet counts should be measured every 2 days during the first week of treatment and then at least weekly until the maintenance dose is reached.

◊ References.

1. Spencer CM, Brogden RN. Anagrelide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of thrombocythaemia. *Drugs* 1994; **47:** 809–22.
2. Chintagumpala MM, *et al.* Treatment of essential thrombocythemia with anagrelide. *J Pediatr* 1995; **127:** 495–8.
3. Petitt RM, *et al.* Anagrelide for control of thrombocythemia in polycythemia and other myeloproliferative disorders. *Semin Hematol* 1997; **34:** 51–4.
4. Oertel MD. Anagrelide, a selective thrombocytopenic agent. *Am J Health-Syst Pharm* 1998; **55:** 1979–86.
5. Lackner H, *et al.* Treatment of children with anagrelide for thrombocythemia. *J Pediatr Hematol Oncol* 1998; **20:** 469–73.
6. Bellucci S, *et al.* Studies of platelet volume, chemistry and function in patients with essential thrombocythaemia treated with anagrelide. *Br J Haematol* 1999; **104:** 886–92.
7. Pescatore SL, Lindley C. Anagrelide: a novel agent for the treatment of myeloproliferative disorders. *Expert Opin Pharmacother* 2000; **1:** 537–46.
8. Dingli D, Tefferi A. Anagrelide: an update on its mechanisms of action and therapeutic potential. *Expert Rev Anticancer Ther* 2004; **4:** 533–41.
9. Steurer M, *et al.* Anagrelide for thrombocytosis in myeloproliferative disorders: a prospective study to assess efficacy and adverse event profile. *Cancer* 2004; **101:** 2239–46.
10. Wagstaff AJ, Keating GM. Anagrelide: a review of its use in the management of essential thrombocythaemia. *Drugs* 2006; **66:** 111–31.

Administration in hepatic impairment. UK licensed drug information recommends that anagrelide should not be given to patients with moderate or severe hepatic impairment. In the USA, anagrelide therapy is not recommended in patients with severe hepatic impairment, although patients with moderate hepatic impairment have been given anagrelide in an initial daily dose of 500 micrograms, which should be maintained for a minimum of 1 week and with cardiovascular monitoring; the daily dose may then be increased cautiously as above.

Preparations

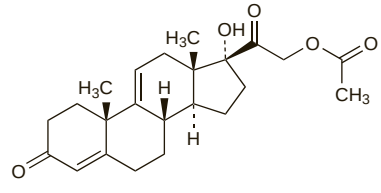
Proprietary Preparations (details are given in Part 3)
Arg.: Agrelid; ***Austral.:*** Agrylin; ***Austria:*** Thromboreductin; ***Belg.:*** Xagrid; ***Braz.:*** Agrylin†; ***Canad.:*** Agrylin; ***Cz.:*** Thromboreductin; Xagrid; ***Denm.:*** Xagrid; ***Fin.:*** Xagrid; ***Fr.:*** Xagrid; ***Ger.:*** Agrylin†; Xagrid; ***Hong Kong:*** Agrylin; Thromboreductin; ***Hung.:*** Thromboreductin; ***Indon.:*** Agrylin; Thromboreductin; ***Irl.:*** Xagrid; ***Israel:*** Agrylin; ***Ital.:*** Xagrid; ***Malaysia:*** Thromboreductin; ***Neth.:*** Xagrid; ***Norw.:*** Xagrid; ***Philipp.:*** Agrylin; ***S.Afr.:*** Agrylin; ***Spain:*** Xagrid; ***Swed.:*** Xagrid; ***Switz.:*** Xagrid; ***UK:*** Xagrid; ***USA:*** Agrylin.

Anecortave *(rINN)*

AL-3789; Anecortava; Anécortave; Anecortave Acetate *(USAN)*; Anecortavum. 17,21-Dihydroxypregna-4,9(11)-diene-3,20-dione 21-acetate.

Анекортав

$C_{23}H_{30}O_5$ = 386.5.
CAS — 7753-60-8.
ATC — S01LA02.
ATC Vet — QS01LA02.



Profile

Anecortave is an angiostatic cortisene under investigation for the treatment of patients with neovascular (wet) age-related macular degeneration (p.785). It is similar in structure to cortisol acetate but without any glucocorticoid activity and is able to inhibit several steps of the neovascularisation process. It is given by posterior juxtascleral depot injection and is available in some countries for compassionate use on a named-patient basis.

◊ References.

1. Clark AF. Mechanism of action of the angiostatic cortisene anecortave acetate. *Surv Ophthalmol* 2007; **52** (suppl 1): S26–S34.
2. Regillo CD, *et al.* Clinical safety profile of posterior juxtascleral depot administration of anecortave acetate 15 mg suspension as primary therapy or adjunctive therapy with photodynamic therapy for treatment of wet age-related macular degeneration. *Surv Ophthalmol* 2007; **52** (suppl 1): S70–S78.
3. Russell SR, *et al.* Anecortave acetate for the treatment of exudative age-related macular degeneration—a review of clinical outcomes. *Surv Ophthalmol* 2007; **52** (suppl 1): S79–S90.
4. Geltzer A, *et al.* Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 08/04/08).