the extent of the benefit is unclear. A cohort study of French children registered to receive growth hormone between 1973 and 1993 suggested that the eventual outcome was not as good as expected, and treated individuals remained short.[8] However, a large American cohort that included more than 11 000 growth-hormone deficient patients found that although treated patients remained below target heights, many did achieve heights within the normal range for chronological age.[9] Maximum growth rates occurred in the first year of treatment and fell progressively thereafter, with no significant difference between growth rates after 4 years compared with pretreatment rates. A further cohort study[10] from the same French register for 1987 to 1996 found that adult heights were similar whether patients completed treatment or stopped before reaching adult height, and that patients with severe growth hormone deficiency may respond better than those with less severe deficiency. Growth hormone treatment regimens have changed over the years, and it appears that with optimal treatment it may be possible for some growth-hormone deficient children to achieve their genetic height potential.[7] An important prognostic factor is age, and for optimum results treatment should be started as early as possible in an attempt to maximise height before the onset of puberty.[2,7]

In patients with multiple pituitary hormone deficiencies, genetic defects in growth hormone synthesis, or severe organic growth hormone deficiency, growth hormone therapy should be continued into adulthood. In other patients, growth hormone deficiency may or may not persist into adult life, and retesting should be done after the patient reaches adult height and after 1 to 3 months without therapy.[2,11] In those patients who need continued treatment, the dose of growth hormone should be gradually reduced in order to maintain IGF-I concentrations within the normal range.[11]

Somatorelin (growth hormone-releasing hormone) or its analogue sermorelin have also been tried to boost growth hormone secretion in patients with growth hormone deficiency. Although there have been reports of improved growth rates, there are limited data directly comparing these with growth hormone. One large study[12] of sermorelin found that, compared with results generally reported for growth hormone therapy, fewer patients responded over a 12-month period and growth responses were poorer. Pralmorelin is a small synthetic growth hormone-releasing peptide that is also under investigation.[13,14]

In patients with Laron dwarfism (growth hormone resistance or insensitivity), conventional growth hormone therapy is ineffective because of defects in the growth hormone receptors. However, replacement therapy with mecasermin, the recombinant form of insulin-like growth factor-I, may be of substantial benefit in the treatment of this disorder.[15]

The use of growth hormone in short stature other than that due to indisputable growth hormone deficiency is controversial. Benefit has been reported from growth hormone therapy in children with chronic renal failure,[16,17] in girls with Turner's syndrome (but see p.2081), in young children (6 months to 3 years of age) with Down's syndrome,[18,19] and in Prader-Willi syndrome[20] (p.2149), all of which are associated with marked growth retardation. However, many commentators see such interventions as essentially cosmetic. The treatment of idiopathic short stature in particular, for which no underlying disorder can be identified, in particular, poses problems as the risks and also the benefits in terms of final height are uncertain.[21] Children who are born small for gestational age usually experience catch-up growth by 2 years of age. In those who do not achieve this, growth hormone therapy can induce catch-up growth and improve childhood height scores; data on adult height are limited, however.[22] Guidelines suggest that therapy is justifiable in chronic renal insufficiency,[3,6,23] Turner's syndrome,[3,6,23] Prader-Willi syndrome,[3,23] and for children born small for gestational age.[3] However, sufficient evidence of benefit is lacking for other disorders including non-growth hormone deficient short stature and growth retardation associated with Down's syndrome, and some[6] consider that growth hormone should not be given to children with constitutional delay of growth. More recently, growth hormone therapy has improved growth rate and height in children with SHOX (short stature homeobox-containing gene) deficiency.[24] Mutations and deletions of the SHOX gene, a gene involved in bone and cartilage formation, are associated with various short stature conditions such as Léri-Weill dyschondrosteosis, and are now understood to play a role in the short stature of Turner's syndrome and in some cases of idiopathic short stature.

Although sex hormones have effects on growth they may also cause premature closure of the epiphyses when given to prepubertal or pubertal children, and this has limited their use. Nonetheless, anabolic drugs such as testosterone and oxandrolone have been used in boys, and oestrogen in girls, who have constitutional delay of growth associated with delayed puberty (see p.2079). Oestrogens are not generally used for growth promotion in girls with Turner's syndrome, but as replacement therapy to promote puberty when a satisfactory height has been reached (see p.2081).

A number of other drugs have been investigated in growth retardation. Clonidine, which can promote growth hormone-releasing hormone release, has been given to children with growth hormone deficiency as well as to short children without proven deficiency, but results have been contradictory and largely unsatisfactory.[25-27] Gonadorelin analogues have also been given with growth hormone to short girls without growth hormone deficiency, in an attempt to slow bone maturation and delay puberty, thereby improving adult height.[28] However, a decrease in bone mineral density may outweigh any modest increase in height.[29] Where growth retardation is associated with zinc deficiency, zinc supplementation may be useful (see p.2000).

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2. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 04/10/05)
3. AACE Growth Hormone Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children—2003 update. *Endocr Pract* 2003; **9:** 64–76. Also available at: http://www.aace.com/pub/pdf/guidelines/hgh.pdf (accessed 05/07/06)
4. van der Sluis IM, *et al.* Long-term effects of growth hormone therapy on bone mineral density, body composition, and serum lipid levels in growth hormone deficient children: a 6-year follow-up study. *Horm Res* 2002; **58:** 207–14.
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6. Drug and Therapeutics Committee, Lawson Wilkins Pediatric Endocrine Society. Guidelines for the use of growth hormone in children with short stature. *J Pediatr* 1995; **127:** 857–67.
7. Harris M, *et al.* Growth hormone treatment in children: review of safety and efficacy. *Pediatr Drugs* 2004; **6:** 93–106.
8. Coste J, *et al.* Long term results of growth hormone treatment in France in children of short stature: population, register based study. *BMJ* 1997; **315:** 708–13.
9. Root AW, *et al.* Effect of long-term recombinant growth hormone therapy in children - the National Cooperative Growth Study, USA, 1985-1994. *J Pediatr Endocrinol Metab* 1998; **11:** 403–12.
10. Carel J-C, *et al.* Adult height after long term treatment with recombinant growth hormone for idiopathic isolated growth hormone deficiency: observational follow up study of the French population based registry. *BMJ* 2002; **325:** 70–3.
11. Wilson TA, *et al.* Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr* 2003; **143:** 415–21.
12. Thorner M. *et al.* Once daily subcutaneous growth hormone-releasing hormone therapy accelerates growth in growth hormone-deficient children during the first year of therapy. *J Clin Endocrinol Metab* 1996; **81:** 1189–96.
13. Mericq V, *et al.* Effects of eight months treatment with graded doses of a growth hormone (GH)-releasing peptide in GH-deficient children. *J Clin Endocrinol Metab* 1998; **83:** 2355–60.
14. Gondo RG, *et al.* Growth hormone-releasing peptide-2 stimulates GH secretion in GH-deficient patients with mutated GH-releasing hormone receptor. *J Clin Endocrinol Metab* 2001; **86:** 3279–83.
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18. Annerén G, *et al.* Normalized growth velocity in children with Down's syndrome during growth hormone therapy. *J Intellect Disabil Res* 1993; **37:** 381–7.
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20. Paterson WF, Donaldson MDC. Growth hormone therapy in the Prader-Willi syndrome. *Arch Dis Child* 2003; **88:** 283–5.
21. Bryant J, *et al.* Recombinant growth hormone for idiopathic short stature in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 23/07/08).
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28. Saggese G, *et al.* Combination treatment with growth hormone and gonadotropin-releasing hormone analogs in short normal girls. *J Pediatr* 1995; **126:** 468–73.
29. Yanovski JA, *et al.* Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med* 2003; **348:** 908–17.

Growth Hormone *(BAN)* ⊗

GH; Phyone; Somatotrophin; Somatotropin; Somatotropina; STH.

Гормон Роста; Соматотропин

CAS — 9002-72-6.

Somatrem *(BAN, USAN, pINN)* ⊗

Met-HGH; Methionyl Human Growth Hormone; Somatremum.

Соматрем

$C_{995}H_{1537}N_{263}O_{301}S_8$ = 22 256.

CAS — 82030-87-3.

ATC — H01AC02.

ATC Vet — QH01AC02.

Description. Somatrem is an analogue of somatropin containing an additional (methionyl) amino-acid residue. It may be produced in bacteria from recombinant DNA.

Sometribove (*BAN*) is methionyl bovine growth hormone.

Sometripor (*BAN*) is methionyl porcine growth hormone.

Somatropin *(BAN, USAN, rINN)* ⊗

CB-311; HGH; Human Growth Hormone; LY-137998; Somatropiini; Somatropina; Somatropinas; Somatropine; Somatropinum; Szomatropin.

Соматропин

$C_{990}H_{1528}N_{262}O_{300}S_7$ = 22 125.

CAS — 12629-01-5.

ATC — H01AC01.

ATC Vet — QH01AC01.

Description. Somatropin is synthetic human growth hormone having the normal structure of the major (22K) component of natural human pituitary growth hormone. It consists of a single polypeptide chain of 191 amino acids with disulfide linkages between positions 53 and 165 and between 182 and 189. For labelling purposes, the name may carry in parentheses an approved code in lower case letters indicative of the method of production: (epr) indicates production by enzymatic conversion of a precursor produced by a bacterium genetically modified by recombinant DNA technology; (rbe) indicates production from bacteria genetically modified by recombinant DNA technology; (rmc) indicates production from genetically engineered and transformed mammalian (mouse) cells.

Somidobove (*BAN*) is synthetic bovine growth hormone.

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

Ph. Eur. 6.2 (Somatropin). A protein having the structure (191 amino acid residues) of the major component of growth hormone produced by the human pituitary. A white or almost white powder, containing not less than 2.5 units/mg. Store at 2° to 8° in airtight containers.

Ph. Eur. 6.2 (Somatropin Concentrated Solution). A clear or slightly turbid, colourless solution. It may contain buffer salts and other auxiliary substances. Store at –20° in airtight containers. Avoid repeated freezing and thawing.

USP 31 (Somatropin). A protein hormone consisting of 191 amino acid residues, and its structure corresponds to the major component of the growth hormone extracted from human pituitary glands. It is produced as a lyophilised powder or bulk solution by methods based on recombinant DNA technology. The lyophilised powder contains not less than 910 micrograms of somatropin per mg, calculated on the anhydrous basis. The bulk solution contains not less than 910 micrograms of somatropin per mg of total protein.

Store at –25° to –10° in airtight containers.

Units

4.4 units of human growth hormone (somatropin) are contained in 1.75 mg of freeze-dried purified human growth hormone, with 20 mg of glycine, 2 mg of mannitol, 2 mg of lactose, and 2 mg of sodium bicarbonate, in one ampoule of the first International Standard (1987).

The second International Standard for Somatropin (2000), rDNA-derived human growth hormone, has a defined content of 1.95 mg of protein per ampoule, with a specific activity of 3.0 units/mg. One mg of anhydrous Somatropin USP is equivalent to 3.0 USP Somatropin Units. Commercial preparations vary somewhat in the number of units/mg.

Adverse Effects and Precautions

Antibodies to growth hormone have been formed in some patients but these rarely seem to affect growth. There may be redness, itching, lumps, or lipoatrophy at the site of injection. Transient dose-related fluid retention with peripheral oedema and carpal tunnel syndrome has occurred; headache, muscle and joint pain, paraesthesia, and cases of benign intracranial hypertension have been reported. Although growth hormone has diabetogenic effects, high acute dosage has been associated with hypoglycaemia followed by hyperglycaemia. Growth hormone therapy may further increase the risk of ear disorders and otitis media in patients with Turner's syndrome, who are already at increased risk of ear and hearing disorders.

Growth hormone therapy is contra-indicated in patients with active neoplasms or intracranial lesions and should be stopped if evidence of tumour growth develops. Growth hormones should not be used for growth promotion in patients with closed epiphyses. Patients with scoliosis should be monitored during growth hormone therapy because of the risk of progression of scoliosis that can occur with rapid growth. Because of the diabetogenic effect of growth hormone it should be given with care to patients with diabetes mellitus; adjustment of antidiabetic therapy may be necessary. Somatropin is contra-indicated in patients with proliferative or preproliferative diabetic retinopathy. Hypothyroidism may develop during treatment, and may result in suboptimal response. Secondary hypoadrenalism may be unmasked by somatropin treatment, requiring glucocorticoid replacement therapy (see also Interactions, below). Growth hormone should not be used in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see also below). For the suggestion that growth hormone should not be used to treat acute catabolic states, as in patients with severe burns or who are otherwise critically ill, see Burns, under Uses and Administration, below.

◊ Reviews.

1. Growth Hormone Research Society. Critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society. *J Clin Endocrinol Metab* 2001; **86:** 1868–70. Also available at: http://jcem.endojournals.org/cgi/reprint/86/5/1868.pdf (accessed 24/10/05)
2. Quigley CA, *et al.* Safety of growth hormone treatment in pediatric patients with idiopathic short stature. *J Clin Endocrinol Metab* 2005; **90:** 5188–96.
3. Bolar K, *et al.* Long-term safety of recombinant human growth hormone in Turner syndrome. *J Clin Endocrinol Metab* 2008; **93:** 344–51.

Abuse. Growth hormone has been subject to abuse in sport for its anabolic effects. However, limited study data suggest that although it may increase lean body-mass, it has minimal effect on strength and athletic performance, and may worsen exercise capacity.[1]

1. Liu H, *et al.* Systematic review: the effects of growth hormone on athletic performance. *Ann Intern Med* 2008; **148:** 747–58.

Benign intracranial hypertension. Benign intracranial hypertension (pseudotumor cerebri) has been described[1,2] in patients given growth hormone treatment. In an analysis[3] of a postmarketing surveillance database (1985 to 2000) of almost 40 000 children and adolescents who had been treated with growth hormone for various conditions, benign intracranial hypertension was more common than in the general paediatric population. The incidence in new patients starting growth hormone therapy was estimated to be about 30 in 100 000, and it had occurred more frequently in patients with renal failure or Turner's syndrome. Headache and papilloedema were the most common symptom and sign, but these did not occur in all patients, and most cases had an onset of a few months. The condition was effectively managed by stopping growth hormone. A small number of patients were rechallenged after the benign intracranial hypertension had resolved, and most could be treated with doses that were 25 to 50% of the original dose. In a report of another case[4] it was pointed out that diagnosis may be complicated by the not infrequent occurrence of headache in patients receiving growth hormone; these normally resolved spontaneously.

1. Malozowski S, *et al.* Growth hormone, insulin-like growth factor I, and benign intracranial hypertension. *N Engl J Med* 1993; **329:** 665–6.
2. Malozowski S, *et al.* Benign intracranial hypertension in children with growth hormone deficiency treated with growth hormone. *J Pediatr* 1995; **126:** 996–9.
3. Reeves GD, Doyle DA. Growth hormone treatment and pseudotumor cerebri: coincidence or close relationship? *J Pediatr Endocrinol Metab* 2002; **15** (suppl 2): 723–30.
4. Price DA, *et al.* Benign intracranial hypertension induced by growth hormone treatment. *Lancet* 1995; **345:** 458–9.

Carcinogenicity. Despite fears to the contrary, studies in children given growth hormone after cranial irradiation for brain tumours or CNS leukaemia have found no evidence that therapy with growth hormone increased the relapse rate.[1-3]

Cases of acute leukaemia have been reported among patients treated with growth hormones. An international workshop convened in 1988 to review known leukaemia cases in patients treated with growth hormones in Europe, North America, Japan, and Australia since 1959 found the observed incidence of leukaemia in growth hormone-treated patients to represent a twofold increase over the expected rate.[4] It was concluded that there may be a small increase in leukaemia incidence associated with growth hormone treatment of growth hormone-deficient patients, but that it was not clear that this was actually attributable to growth hormone. A later study involving 6284 patients treated with growth hormone between 1963 and 1985 in the USA confirmed an increase of about 2.5-fold in the incidence of leukaemia in this population, but noted that many of the patients had other risk factors for leukaemia.[5] It has been suggested that growth hormone deficiency is itself a risk factor for leukaemia and that perhaps this, rather than growth hormone treatment, is related to the increased incidence of leukaemia in these patients.[6] If there is any risk it is relatively small, and in view of the essential nature of growth hormone therapy in growth hormone-deficient children it was considered inappropriate and unwise to withhold it.[4] Further large cohort studies of survivors of childhood cancers[3] or patients treated for idiopathic growth hormone deficiency[7] have found that the use of growth hormone was not associated with an increased risk of leukaemia.

There is some evidence to suggest that growth hormone may increase the risk of solid tumours. The risk of secondary solid tumours was increased in a cohort of childhood cancer survivors, but the authors considered that the risk was probably quite small compared with the benefits of growth hormone therapy in these patients.[3] Another cohort of patients who had been treated for idiopathic growth hormone deficiency showed increased risks in the incidence and mortality of colorectal cancer.[7]

Further reports of malignancies associated with growth hormone therapy include two children with Bloom's syndrome (a rare chromosomal disorder affecting DNA replication), one of whom developed B-cell non-Hodgkin's lymphoma and the other stem-cell leukaemia.[8]

Continued surveillance of patients who have received growth hormone therapy has been encouraged.[9]

1. Packer RJ, *et al.* Growth hormone replacement therapy in children with medulloblastoma: use and effect on tumor control. *J Clin Oncol* 2001; **19:** 480–7.
2. Swerdlow AJ, *et al.* Growth hormone treatment of children with brain tumors and risk of tumor recurrence. *J Clin Endocrinol Metab* 2000; **85:** 4444–9.
3. Sklar CA, *et al.* Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* 2002; **87:** 3136–411.
4. Fisher DA, *et al.* Leukaemia in patients treated with growth hormone. *Lancet* 1988; **i:** 1159–60.
5. Fradkin JE, *et al.* Risk of leukemia after treatment with pituitary growth hormone. *JAMA* 1993; **270:** 2829–32.
6. Rapaport R, *et al.* Relationship of growth hormone deficiency and leukemia. *J Pediatr* 1995; **126:** 759–61.
7. Swerdlow AJ, *et al.* Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: a cohort study. *Lancet* 2002; **360:** 273–7.
8. Brock PR, *et al.* Malignant disease in Bloom's syndrome children treated with growth hormone. *Lancet* 1991; **337:** 1345–6.
9. Ogilvy-Stuart AL, Gleeson H. Cancer risk following growth hormone use in childhood: implications for current practice. *Drug Safety* 2004; **27:** 369–82.

Creutzfeldt-Jakob disease. Reports in 1985 of a small number of deaths from Creutzfeldt-Jakob disease in patients under 40 years of age who had received growth hormone extracted from human pituitary glands resulted in the suspension of the distribution of pituitary-derived growth hormone by the licensing authorities in a number of countries, including Australia, Canada, the Netherlands, the UK, and the USA. Preparations of non-pituitary-derived growth hormone are now available that are free from contamination with Creutzfeldt-Jakob agent. However, because of the long incubation period of the disease, cases are still being reported in patients who had received pituitary-derived growth hormone years previously.[1-4]

1. Brown P, *et al.* Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology* 2000; **55:** 1075–81.
2. Croes EA, *et al.* Creutzfeldt-Jakob disease 38 years after diagnostic use of human growth hormone. *J Neurol Neurosurg Psychiatry* 2002; **72:** 792–3.
3. Swerdlow AJ, *et al.* Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone. *Neurology* 2003; **61:** 783–91.
4. Hirst C. Iatrogenic Creutzfeldt-Jakob disease presenting 24 years after human growth hormone administration. *Br J Hosp Med* 2005; **66:** 592–3.

Effects on carbohydrate metabolism. A retrospective analysis[1] of data from a pharmacoepidemiological survey of children treated with growth hormone found a higher incidence of type 2 diabetes, compared with that found in untreated children. The researchers speculated that growth hormone treatment might precipitate the onset of type 2 diabetes in predisposed patients, and proposed that patients with risk factors for diabetes, including Turner's syndrome, Prader-Willi syndrome, or intrauterine growth retardation, be monitored. Studies of growth hormone have reported rises in serum concentrations of insulin, fasting and postprandial blood-glucose, and glycosylated haemoglobin, although these changes were generally small.[2] It has been noted that these effects appear to regress during treatment, but not always, and in some patients glucose intolerance or diabetes mellitus are not reversible after withdrawal of growth hormone.

Nonketotic hyperglycaemia developed within weeks of beginning growth hormone therapy in a 22-month-old child, leading to convulsions and metabolic acidosis; the patient died despite correction of the hyperglycaemia.[3]

1. Cutfield WS, *et al.* Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet* 2000; **355:** 610–13.
2. Jeffcoate W. Growth hormone therapy and its relationship to insulin resistance, glucose intolerance and diabetes mellitus: a review of recent evidence. *Drug Safety* 2002; **25:** 199–212.
3. Garg AK, Hyperglycemia during replacement growth hormone therapy. *J Pediatr* 1994; **125:** 329.

Effects on immune function. Growth hormone is generally considered to interact with the immune system although there is a lack of evidence that this is clinically significant.[1-4] There has been a report of acute renal transplant rejection in 2 children receiving treatment for growth retardation with somatropin.[5] In both children renal function of the transplant was stable for several years before somatropin was started, and growth hormone therapy had continued for some months before rejection occurred. It was suggested that during the first months of growth hormone therapy in transplant recipients, immunosuppressive therapy should be increased and transplant function carefully monitored. However, in subsequent studies[6,7] the use of growth hormone did not affect the incidence of rejection.

1. Church JA, *et al.* Immune functions in children treated with biosynthetic growth hormone. *J Pediatr* 1989; **115:** 420–3.
2. Rapaport R, Oleske J. Immune function during growth hormone therapy. *J Pediatr* 1990; **116:** 669–70.
3. Rekers-Mombarg LTM, *et al.* Immunologic studies in children with idiopathic short stature before and during growth hormone therapy. *Horm Res* 1995; **44:** 203–7.
4. Lebl J, *et al.* Immune system in adults with childhood-onset growth hormone deficiency: effect of growth hormone therapy. *Endocr Regul* 2000; **34:** 169–73.
5. Tydén G, *et al.* Acute renal graft rejection after treatment with human growth hormone. *Lancet* 1990; **336:** 1455–6.
6. Maxwell H, Rees L. Randomised controlled trial of recombinant human growth hormone in prepubertal and pubertal renal transplant recipients. *Arch Dis Child* 1998; **79:** 481–7.
7. Maxwell H, *et al.* Growth hormone and markers of immune function in children with renal transplants. *Pediatr Nephrol* 2000; **14:** 473–5.

Effects on the pancreas. A report of acute pancreatitis on starting growth hormone treatment in a patient with pseudohypoparathyroidism and growth hormone deficiency.[1] Ten further cases of acute pancreatitis associated with growth hormone treatment had been reported to the FDA at the time of writing.

1. Malozowski S, *et al.* Acute pancreatitis associated with growth hormone therapy for short stature. *N Engl J Med* 1995; **332:** 401–2.

Effects on skeletal muscle. A report of mild inflammatory myositis, with myalgia and muscle weakness, in 2 patients receiving growth hormone therapy.[1] It was suggested that the effect might be due to *m*-cresol used as a preservative in the preparation.

1. Yordam N. Myositis associated with growth hormone therapy. *J Pediatr* 1994; **125:** 671.

Gynaecomastia. A report of 22 cases of prepubertal gynaecomastia diagnosed during growth hormone treatment.[1]

1. Malozowski S, Stadel BV. Prepubertal gynecomastia during growth hormone therapy. *J Pediatr* 1995; **126:** 659–61.

Hypersensitivity. Generalised urticaria in a patient given somatropin was overcome by a desensitisation regimen.[1] The patient was subsequently maintained uneventfully on daily injections of somatropin.

1. Walker SB, *et al.* Systemic reaction to human growth hormone treated with acute desensitization. *Pediatrics* 1992; **90:** 108–9.

Iron deficiency. The view has been expressed[1] that given the increased production of haemoglobin and the prevalence of iron deficiency in patients treated with growth hormone, supplemen-

tation with iron should be considered in patients receiving growth hormone treatment.

1. Vihervuori E, *et al.* Increases in hemoglobin concentration and iron needs in response to growth hormone treatment. *J Pediatr* 1994; **125:** 242–5.

Prader-Willi syndrome. One US manufacturer of somatropin has stated that as of April 2003 it was aware of 7 reports of death in children with Prader-Willi syndrome treated with growth hormone.[1] The patients shared one or more of the following risk factors: severe obesity, a history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. It was recommended that patients with Prader-Willi syndrome should be evaluated for upper airway obstruction, before beginning treatment, and if signs of such obstruction, such as snoring, developed during treatment therapy should be suspended. Somatropin was considered contra-indicated in these patients if they were severely obese or had severe respiratory impairment; licensed drug information in the USA had been amended accordingly. Early diagnosis and aggressive treatment of respiratory infections was also recommended. A few cases have been described in the literature.[2-4]

Children with Prader-Willi syndrome appear to have a higher incidence of respiratory problems such as sleep apnoea, hypoventilation, and infections than healthy children.[5] A prospective study[6] of 25 patients reported that sleep-disordered breathing had actually improved in most of them after 6 weeks of growth hormone therapy. However, there was a subgroup of 6 patients in which obstructive sleep apnoea and hypopnoea worsened; 4 of them had developed upper respiratory-tract infections and enlarged tonsils, and 2 had high serum concentrations of insulin-like growth factor I (IGF-I) and enlarged tonsils.

1. Pharmacia, USA. 2003 Safety alert: Genotropin (somatropin [rDNA origin] for injection). Available at: http://www.fda.gov/medwatch/SAFETY/2003/genotropin.htm (accessed 14/06/07)
2. Eiholzer U, *et al.* Fatal outcome of sleep apnoea in PWS during the initial phase of growth hormone treatment: a case report. *Horm Res* 2002; **58** (suppl 3): 24–6.
3. Van Vliet G, *et al.* Sudden death in growth hormone-treated children with Prader-Willi syndrome. *J Pediatr* 2004; **144:** 129–31.
4. Craig ME, *et al.* Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). *Clin Endocrinol (Oxf)* 2006; **65:** 178–85.
5. Eiholzer U. Deaths in children with Prader-Willi syndrome: a contribution to the debate about the safety of growth hormone treatment in children with PWS. *Horm Res* 2005; **63:** 33–9.
6. Miller J, *et al.* Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab* 2006; **91:** 413–17.

Interactions

High doses of corticosteroids may inhibit the growth promoting effects of growth hormone. Doses of growth hormone may need to be increased in women receiving oral oestrogen replacement therapy, and may require adjustment if the route of oestrogen administration is changed.

Pharmacokinetics

Somatropin is well absorbed after subcutaneous or intramuscular injection with a bioavailability varying from about 60 to 80%; peak serum concentrations may not be achieved for several hours. After intravenous injection it has a half-life of about 20 to 30 minutes but after subcutaneous or intramuscular doses serum concentrations decline with a half-life of 3 to 5 hours, due to more prolonged release from the injection site. It is metabolised in the liver and kidneys and excreted in bile.

Absorption. Studies of the pharmacokinetics of somatropin after transdermal jet injection from 2 devices in healthy subjects suggested that absorption was more rapid and peak serum concentration higher than after conventional subcutaneous injection of the same dose.[1,2] However this did not seem to result in any difference in the total amount absorbed, nor in the biological effect. A third device[3] provided a similar concentration-time profile for somatropin compared with conventional injection in healthy subjects. When studied in children with growth hormone deficiency, however, this device was considered to cause more bleeding, pain, soreness, and bruising at the injection site than a needle-injection pen device.

1. Verhagen A, *et al.* Pharmacokinetics and pharmacodynamics of a single dose of recombinant human growth hormone after subcutaneous administration by jet-injection: comparison with conventional needle-injection. *Eur J Clin Pharmacol* 1995; **49:** 69–72.
2. Agersø H, *et al.* Pharmacokinetics and pharmacodynamics of a new formulation of recombinant human growth hormone administered by ZomaJet 2 Vision, a new needle-free device, compared to subcutaneous administration using a conventional syringe. *J Clin Pharmacol* 2002; **42:** 1262–8.
3. Dörr HG, *et al.* Are needle-free injections a useful alternative for growth hormone therapy in children? Safety and pharmacokinetics of growth hormone delivered by a new needle-free injection device compared to a fine gauge needle. *J Pediatr Endocrinol Metab* 2003; **16:** 383–92.

Uses and Administration

Somatropin is synthetic human growth hormone and somatrem its methionyl analogue.

Growth hormone is an anabolic hormone secreted by the anterior lobe of the pituitary, varying in size and amino-acid sequence between animal species. It promotes growth of skeletal, muscular, and other tissues, stimulates protein anabolism, and affects fat and mineral metabolism. The hormone has a diabetogenic action on carbohydrate metabolism. Secretion is pulsatile and dependent on neural and hormonal influences including a hypothalamic release-inhibiting hormone (see Somatostatin, p.1809), and a hypothalamic releasing hormone (see Somatorelin, p.1808). Sleep, hypoglycaemia, and physical or emotional stress result in increased secretion of growth hormone. The effects of growth hormone on skeletal growth are mediated by the somatomedins (see p.1807).

Somatropin or somatrem is given to children with open epiphyses for the treatment of short stature due to growth hormone deficiency (pituitary dwarfism) following assessment of pituitary function. Somatropin is also used in children with some other forms of growth retardation, such as that associated with Turner's syndrome, Noonan syndrome, SHOX (short stature homeobox-containing gene) deficiency, or chronic renal insufficiency, in short children born small for gestational age, and in idiopathic short stature. In Prader-Willi syndrome, somatropin is given to improve growth and body composition (but see also under Adverse Effects and Precautions, above). In adults, somatropin is given for confirmed growth hormone deficiency. It is also used in the management of wasting or cachexia associated with AIDS. In short bowel syndrome, somatropin is used to increase intestinal absorption of water, electrolytes, and nutrients from specialised nutritional support.

Doses should be individualised for each patient. Manufacturers vary somewhat in their estimates of the number of units/mg for somatropin and although some countries specify labelling in mg, others require labelling in units or both. Somatrem has been given in doses similar to those of somatropin, but is no longer generally available.

In *children with growth hormone deficiency*, the usual daily dose in the UK is 25 to 35 micrograms/kg by subcutaneous injection (0.07 to 0.1 units/kg), or 0.7 to 1 mg/m^2 (2 to 3 units/m^2). Similar doses are used in other countries, by subcutaneous or intramuscular injection, and the total weekly dose may be divided into 3, 6, or 7 doses. A suspension of somatropin for subcutaneous depot injection has also been used, given in a dose of 1.5 mg/kg on the same day of each month. Alternatively, the dose could be given as 750 micrograms/kg twice monthly (for example, on days 1 and 15 of each month).

In *Turner's syndrome* (gonadal dysgenesis), a subcutaneous daily dose of 45 to 50 micrograms/kg (0.14 units/kg), or 1.4 mg/m^2 (4.3 units/m^2), may be used, although higher doses of up to 67 micrograms/kg daily have been licensed for use in the USA. Doses of up to 66 micrograms/kg daily have been used for growth retardation related to *Noonan syndrome*. Daily doses of 45 to 50 micrograms/kg may be used in children with growth retardation due to *chronic renal insufficiency* or *SHOX deficiency*.

In children with growth retardation who were *born small for gestational age*, the licensed daily dose in the UK is 35 micrograms/kg by subcutaneous injection (0.1 units/kg), or 1 mg/m^2 (3 units/m^2). In the USA, the licensed dose is somewhat higher, at 480 micrograms/kg weekly, divided into 6 or 7 doses.

In children with *idiopathic short stature* somatropin is given subcutaneously in a weekly dose of up to 300 to 470 micrograms/kg divided into 6 or 7 doses.

In children with *Prader-Willi syndrome*, a daily dose of about 35 micrograms/kg, or 1 mg/m^2, is given subcutaneously; daily doses should not exceed 2.7 mg.

In *adults with growth hormone deficiency* lower doses are recommended. The initial dose is not more than 6 micrograms/kg (0.018 units/kg) subcutaneously daily. The dose can then be gradually increased according to patient response, to a usual maximum of 12.5 micrograms/kg daily. Alternatively, an initial dose in the range of 150 to 300 micrograms daily (0.45 to 0.9 units) is increased gradually at monthly intervals, based on clinical response, to a maintenance dose of no more than 1 mg daily. Dosage requirements may decline with increasing age. In the UK, it has been recommended that treatment should be re-assessed 9 months after starting therapy.

In the treatment of *HIV-associated wasting or cachexia* somatropin is given in doses of 100 micrograms/kg daily by subcutaneous injection at bedtime, to a maximum of 6 mg daily. A starting dose of 100 micrograms/kg on alternate days may be considered for patients who are at increased risk of adverse effects.

In *short bowel syndrome* somatropin is given subcutaneously in a dose of about 100 micrograms/kg daily (to a maximum of 8 mg daily) for 4 weeks.

Administration in adults. Growth hormone continues to be secreted in adult life, although secretion and activity gradually decline with increasing age, and it appears to play a role in maintaining skeletal and lean body-mass amongst other things. In adults with growth hormone deficiency (usually secondary to pituitary adenoma or its treatment) replacement therapy with growth hormone is reported to decrease body fat and abdominal adiposity, increase lean body-mass, and improve lipid profiles.[1-4] It may also increase bone density,[1,3] but many studies have been uncontrolled and of short duration, and any beneficial effect on bone density appears to be small.[5] Strength and exercise capacity can also be improved, although prolonged growth hormone therapy and physical training may be required to increase muscle performance.[3] Cardiac structure and function can be adversely affected by growth hormone deficiency, and replacement therapy in adults can have a positive effect on some cardiac parameters.[6] There are also some reports of improvements in quality of life;[3] although a study[7] using general standardised psychometric tests found no benefit, another[8] using a questionnaire developed for adults with hypopituitarism reported long-term benefits. Long-term data are not yet available to determine whether growth hormone therapy reduces the mortality rate in this group of patients, but it may provide some protection against myocardial infarction.[9] Guidelines on the use of growth hormone in adults with growth hormone deficiency have been issued.[10-13]

Less well established is the use of growth hormone in otherwise healthy elderly patients. Considerable controversy has attended suggestions that growth hormone therapy may retard or reverse some of the metabolic effects of ageing, and there is some concern that these patients may be at increased risk of adverse effects.[14] Studies[15] have shown that growth hormone can increase lean body-mass and decrease body fat, but functional ability does not necessarily improve and common adverse effects include peripheral oedema, carpal tunnel syndrome, arthralgias, and gynaecomastia.

Other uses for growth hormone in adult patients are discussed below.

1. Götherström G, *et al.* A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab* 2001; **86:** 4657–65.
2. Attanasio AF, *et al.* Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status—3-year results from the HypoCCS Database. *J Clin Endocrinol Metab* 2002; **87:** 1600–6.
3. Verhelst J, Abs R. Long-term growth hormone replacement therapy in hypopituitary adults. *Drugs* 2002; **62:** 2399–2412.
4. Maison P, *et al.* Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. *J Clin Endocrinol Metab* 2004; **89:** 2192–9.
5. Davidson P, *et al.* Growth hormone replacement in adults and bone mineral density: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2004; **60:** 92–8.
6. Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. *Circulation* 2003; **108:** 2648–52.
7. Baum HBA, *et al.* Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. *J Clin Endocrinol Metab* 1998; **83:** 3184–9.
8. Rosilio M, *et al.* Long-term improvement of quality of life during growth hormone (GH) replacement therapy in adults with GH deficiency, as measured by questions on life satisfaction-hypopituitarism (QLS-H). *J Clin Endocrinol Metab* 2004; **89:** 1684–93.

9. Svensson J, *et al.* Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. *J Clin Endocrinol Metab* 2004; **89:** 3306–12.
10. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. *J Clin Endocrinol Metab* 1998; **83:** 379–81. Also available at: http://www.ghresearchsociety.org/files/PortStevens.pdf (accessed 04/10/05)
11. AACE Growth Hormone Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children—2003 update. *Endocr Pract* 2003; **9:** 64–76. Also available at: http://www.aace.com/pub/pdf/guidelines/hgh.pdf (accessed 05/07/06)
12. NICE. Human growth hormone (somatropin) in adults with growth hormone deficiency: Technology Appraisal 64 (issued August 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/TA64_HGHadults_fullguidance.pdf (accessed 20/08/08)
13. Molitch ME, *et al.* Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006; **91:** 1621–34. Also available at: http://www.endo-society.org/guidelines/final/upload/042506_CG_HormoneBook.pdf (accessed 20/08/08)
14. Vance ML. Can growth hormone prevent aging? *N Engl J Med* 2003; **348:** 779–80.
15. Liu H, *et al.* Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Ann Intern Med* 2007; **146:** 104–15.

Burns. In children with severe burns requiring skin grafts, somatropin 200 micrograms/kg daily by intramuscular injection reduced donor-site healing times and hospitalisation times; subcutaneous somatropin 100 micrograms/kg daily was ineffective.[1] There has been some concern that growth hormone therapy might increase hypertrophic scar formation, but a study[2] of somatropin 50 micrograms/kg daily for 1 year after hospital discharge did not find this. Somatropin treatment given during hospitalisation has also been reported to ameliorate burn-induced growth delays in such children; those injured during non-growth-spurt years may benefit most.[3,4] Long-term therapy given for 1 year after wound healing may also improve weight, linear growth, lean body-mass, and bone mineral content.[5] However, the manufacturers have recommended that somatropin should not be used to treat acute catabolic states in critically ill and burn patients, as there is some evidence in adults that mortality may be increased.[6] The management of burns is described on p.1578.

1. Herndon DN, *et al.* Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg* 1990; **212:** 424–9.
2. de Oliveira GV, *et al.* Growth hormone effects on hypertrophic scar formation: a randomized controlled trial of 62 burned children. *Wound Repair Regen* 2004; **12:** 404–11.
3. Low JFA, *et al.* Effect of growth hormone on growth delay in burned children: a 3-year follow-up study. *Lancet* 1999; **354:** 1789.
4. Low JFA, *et al.* The effect of short-term growth hormone treatment on growth and energy expenditure in burned children. *Burns* 2001; **27:** 447–52.
5. Hart DW, *et al.* Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. *Ann Surg* 2001; **233:** 827–34.
6. Takala J, *et al.* Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; **341:** 785–92.

Cachexia and lipodystrophy. Treatment with subcutaneous growth hormone has been reported[1,2] to reverse weight loss and improve body wasting in subjects with HIV disease (p.858). It can have beneficial effects on physical function, body-weight, lean body-mass, and measures of health-related quality of life.[3]

Some benefit has been reported[4-8] with growth hormone therapy in HIV-associated lipodystrophy.

Growth hormone therapy has also been reported to improve metabolic indicators of malnutrition in some[9] but not other[10] studies of patients undergoing haemodialysis.

1. Schambelan M, *et al.* Recombinant human growth hormone in patients with HIV-associated wasting: a randomized, placebo-controlled trial. *Ann Intern Med* 1996; **125:** 873–82.
2. Moyle GJ, *et al.* Growth hormone improves lean body mass, physical performance, and quality of life in subjects with HIV-associated weight loss or wasting on highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2004; **35:** 367–75.
3. Goldsmith DR, Wagstaff AJ. Mammalian cell-derived somatropin: a review of its use in the management of HIV-associated wasting. *Drugs* 2006; **66:** 387–401.
4. Lo JC, *et al.* The effects of recombinant human growth hormone on body composition and glucose metabolism in HIV-infected patients with fat accumulation. *J Clin Endocrinol Metab* 2001; **86:** 3480–7.
5. Tai VW, *et al.* Effects of recombinant human growth hormone on fat distribution in patients with human immunodeficiency virus–associated wasting. *Clin Infect Dis* 2002; **35:** 1258–62.
6. Kotler DP, *et al.* Effects of growth hormone on abnormal visceral adipose tissue accumulation and dyslipidemia in HIV-infected patients. *J Acquir Immune Defic Syndr* 2004; **35:** 239–52. Correction. *ibid.* 2006; **43:** 378–81.
7. Lo JC, *et al.* The effects of low-dose growth hormone in HIV-infected men with fat accumulation: a pilot study. *Clin Infect Dis* 2004; **39:** 732–5.
8. Grunfeld C, *et al.* Recombinant human growth hormone to treat HIV-associated adipose redistribution syndrome: 12 week induction and 24-week maintenance therapy. *J Acquir Immune Defic Syndr* 2007; **45:** 286–97.
9. Johannsson G, *et al.* Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis: anabolic effect and functional improvement. *Am J Kidney Dis* 1999; **33:** 709–17.
10. Kotzmann H, *et al.* One-year growth hormone therapy improves granulocyte function without major effects on nutritional and anthropometric parameters in malnourished hemodialysis patients. *Nephron Clin Pract* 2003; **93:** c75–82.

Cardiovascular disorders. A few small uncontrolled studies have reported improvements in heart failure (p.1165) with the use of growth hormone.[1] A meta-analysis[2] of 12 studies using growth hormone in adults with chronic heart failure, including 8 placebo-controlled studies, also found evidence for improvement in several cardiovascular measures; however, individual results have been mixed and further study of long-term high-dose therapy is needed. A small underpowered study[3] of 6 months of treatment in children with dilated cardiomyopathy found only a trend towards improved cardiac function. Retrospective analysis[4] of a group of childhood cancer survivors found that growth hormone used to treat deficiency had some beneficial effects on anthracycline-induced left ventricular dysfunction, but that these diminished when growth hormone therapy was stopped.

1. Volterrani M, *et al.* Role of growth hormone in chronic heart failure: therapeutic implications. *Drugs* 2000; **60:** 711–19.
2. Le Corvoisier P, *et al.* Cardiac effects of growth hormone treatment in chronic heart failure: a meta-analysis. *J Clin Endocrinol Metab* 2007; **92:** 180–5.
3. McElhinney DB, *et al.* Recombinant human growth hormone treatment for dilated cardiomyopathy in children. Abstract: *Pediatrics* 2004; **114:** 1074–5. Full version: http://pediatrics.aappublications.org/cgi/content/full/114/4/e452 (accessed 16/09/05)
4. Lipshultz SE, *et al.* Cardiac changes associated with growth hormone therapy among children treated with anthracyclines. *Pediatrics* 2005; **115:** 1613–22.

Fibromyalgia. Symptomatic improvement was reported after several months in a study of daily subcutaneous growth hormone injection in women with fibromyalgia,[1] a painful form of soft-tissue rheumatism (p.13), and low levels of insulin-like growth factor I (IGF-I).

1. Bennett RM, *et al.* A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. *Am J Med* 1998; **104:** 227–31.

Growth retardation. Growth hormone is a mainstay of the management of growth retardation[1] (p.1798) and guidelines[2-6] have been issued concerning its appropriate use.

1. Harris M, *et al.* Growth hormone treatment in children: review of safety and efficacy. *Pediatr Drugs* 2004; **6:** 93–106.
2. Drug and Therapeutics Committee, Lawson Wilkins Pediatric Endocrine Society. Guidelines for the use of growth hormone in children with short stature. *J Pediatr* 1995; **127:** 857–67.
3. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; **85:** 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 04/10/05)
4. NICE. Guidance on the use of human growth hormone (somatropin) in children with growth failure: Technology Appraisal 42 (May 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/HGHinChild-42-ALS.pdf (accessed 20/08/08)
5. Wilson TA, *et al.* Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr* 2003; **143:** 415–21.
6. AACE Growth Hormone Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children—2003 update. *Endocr Pract* 2003; **9:** 64–76. Also available at: http://www.aace.com/pub/pdf/guidelines/hgh.pdf (accessed 05/07/06)

Infertility. Growth hormone appears to sensitise the ovary to stimulation by gonadotrophins and it has been suggested that somatropin may have a role in the management of female infertility. However, studies of somatropin added to gonadotrophin regimens have generally been small, used different treatment protocols and outcome measures, and studied mixed groups of women in terms of the cause of infertility. Studies of women with poor response to ovarian stimulation have shown mixed results, and response may depend on the cause of infertility. Mixed results have also been reported in women with polycystic ovary syndrome. Benefits may be most likely in women with hypogonadotrophic hypogonadism,[1] but there is no additional benefit for women who have a normal ovarian response to gonadotrophins.[1,2] UK guidelines[3] for the treatment of infertility do not recommend its use. Growth hormone has also been tried similarly to enhance spermatogenesis in infertile men unresponsive to conventional therapy, but studies have been small, and despite some encouraging reports[4] others have found no benefit.[5,6]

For a discussion of infertility and the more usual drugs used in its management, see p.2080.

1. Artini PG, *et al.* Growth hormone cotreatment with gonadotropins in ovulation induction. *J Endocrinol Invest* 1996; **19:** 763–79.
2. Harper K, *et al.* Growth hormone for in vitro fertilization. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 16/09/05).
3. National Collaborating Centre for Women's and Children's Health/National Institute for Clinical Excellence. Fertility: assessment and treatment for people with fertility problems (issued February 2004). Available at: http://www.rcog.org.uk/resources/Public/pdf/Fertility_full.pdf (accessed 24/07/08) or http://www.nice.org.uk/nicemedia/pdf/CG011fullguideline.pdf (accessed 24/07/08)
4. Shoham Z, *et al.* Cotreatment with growth hormone for induction of spermatogenesis in patients with hypogonadotropic hypogonadism. *Fertil Steril* 1992; **57:** 1044–51.
5. Ovesen PG. *et al.* Vaekstthormonbehandling af maend med nedsat saedkvalitet. *Ugeskr Laeger* 1998; **160:** 176–80.
6. Giagulli VA. Absence of effect of recombinant growth hormone to classic gonadotropin treatment on spermatogenesis of patients with severe hypogonadotropic hypogonadism. *Arch Androl* 1999; **43:** 47–53.

Osteogenesis imperfecta. For reference to possible benefit from growth hormone therapy in patients with osteogenesis imperfecta, see p.1083.

Osteomalacia. As mentioned on p.1084, there has been some interest in the use of growth hormone in children with hypophosphataemic rickets.

Prader-Willi syndrome. Growth hormone treatment may be of benefit in the management of Prader-Willi syndrome (p.2149). It increases growth velocity and improves body composition, by reducing fat mass and increasing muscle mass. However, there is limited information about long-term efficacy, and the effect on growth velocity is reported to wane after 1 to 3 years of therapy. There are also specific contra-indications and precautions relating to the use of growth hormone in these patients (see under Adverse Effects and Precautions, above).

References.

1. Carrel AL, *et al.* Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: a controlled study. *J Pediatr* 1999; **134:** 215–21.
2. Myers SE, *et al.* Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome. *J Pediatr* 2000; **137:** 42–9.
3. Burman P, *et al.* Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev* 2001; **22:** 787–99.
4. Carrel AL, *et al.* Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. *J Clin Endocrinol Metab* 2002; **87:** 1581–5.
5. Whitman BY, *et al.* The behavioral impact of growth hormone treatment for children and adolescents with Prader-Willi syndrome: a 2-year, controlled study. Abstract: *Pediatrics* 2002; **109:** 308–9. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/2/e35 (accessed 16/09/05)
6. Paterson WF, Donaldson MDC. Growth hormone therapy in the Prader-Willi syndrome. *Arch Dis Child* 2003; **88:** 283–5.
7. Carrel AL, *et al.* Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr* 2004; **145:** 744–9.
8. Craig ME, *et al.* Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). *Clin Endocrinol (Oxf)* 2006; **65:** 178–85.
9. Myers SE, *et al.* Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits. *Am J Med Genet A* 2007; **143:** 443–8.

Short bowel syndrome. A combination of growth hormone, glutamine, and dietary modification may improve intestinal absorption of fluid, electrolytes, and other nutrients, and thus reduce parenteral nutrition requirements in patients with short bowel syndrome.[1] However, studies have produced conflicting results, and benefit may depend on a number of factors including the type and length of remaining bowel, the presence or absence of mucosal disease, and the doses of somatropin and glutamine.[2]

1. Keating GM, Wellington K. Somatropin (Zorbtive) in short bowel syndrome. *Drugs* 2004; **64:** 1375–81.
2. Matarese LE, *et al.* Growth hormone, glutamine, and modified diet for intestinal adaptation. *J Am Diet Assoc* 2004; **104:** 1265–72.

Veterinary and agricultural use. Bovine growth hormone or bovine somatotrophin (bovine somatotropin; BST) can increase milk yield in dairy cows. There has been considerable debate about both animal welfare and human food safety, and although it is approved in the USA[1] its use is banned in the EU.[2]

1. FDA. CVM Update. Update on human safety of BST (February 5th, 1999). Available at: http://www.fda.gov/cvm/CVM_updates/BSTSAFUP.html (accessed 16/09/05)
2. Anonymous. Public health and consumer protection: animal welfare 1.2.220. Bulletin EU 12-1999. Available at: http://europa.eu/bulletin/en/9912/p102220.htm (accessed 05/07/06)

Preparations

BP 2008: Somatropin Injection;
Ph. Eur.: Somatropin for Injection;
USP 31: Somatropin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Biotropin; Genotropin; HHT; Hutrope; Norditropin; Saizen; Serostim†; ***Austral.:*** Genotropin; Humatro-Pen†; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Scitropin; ***Austria:*** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; ***Belg.:*** Genotonorm; Humatrope; Norditropin; NutropinAq; Zomacton; ***Braz.:*** Biotropin†; Eutropin; Genotropin; Hormotrop; Humatrope; Norditropin; Saizen; Somatrop; ***Canad.:*** Humatrope; Nutropin; Protropin†; Saizen; Serostim; ***Chile:*** Genotonorm; HHT; Humatrope; Hutrope; Norditropin; Saizen†; ***Cz.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Valtropin; Zomacton; ***Denm.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Zomacton; ***Fin.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; ***Fr.:*** Genotonorm; Maxomat; Norditropine; NutropinAq;

Saizen; Umatrope; Zomacton; ***Ger.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; ***Gr.:*** Genotropin; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; ***Hong Kong:*** Genotropin; Humatrope; Norditropin; Saizen; Scitropin; Serostim; ***Hung.:*** Genotropin; Humatrope; Norditropin; Nutropin; Saizen†; Zomacton†; ***India:*** Saizen; ***Indon.:*** Eutropin; Genotropin; Norditropin; Saizen; ***Irl.:*** Genotropin; Norditropin; Saizen; Zomacton; ***Israel:*** Bio-Tropin; Genotropin; Norditropin; ***Ital.:*** Genotropin; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; ***Jpn:*** Growject; Norditropin; ***Malaysia:*** Genotropin; Norditropin; Saizen; ***Mex.:*** Cryo-Tropin; Genotropin; HHT; Humatrope; Norditropin; Saizen; Serostim; ***Neth.:*** Genotropin; Humatrope; Norditropin; Nutropin; Zomacton; ***Norw.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; ***NZ:*** Genotropin; Norditropin; Saizen; ***Philipp.:*** GenHeal; Humatrope; Norditropin; Saizen; SciTropin; ***Pol.:*** Genotropin; ***Port.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Omnitrope; Saizen; Valtropin; Zomacton; ***Rus.:*** Genotropin (Генотропин); Humatrope (Хуматрон); Norditropin (Нордитропин); Saizen (Сайзен); ***S.Afr.:*** Genotropin; Humatrope; Norditropin; Saizen†; ***Singapore:*** Genotropin; Humatrope†; Norditropin; Saizen; Scitropin†; ***Spain:*** Genotonorm; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; ***Swed.:*** Genotropin; Humatrope; Norditropin; NutropinAq; Saizen; Zomacton; ***Switz.:*** Genotropin; Humatrope; Norditropine; Saizen; ***Thai.:*** Saizen; ***Turk.:*** Genotropin; Humatrope; Norditropin; Saizen; Zomacton; ***UK:*** Genotropin; Humatrope; Norditropin; Nutropin; Saizen; Zomacton; ***USA:*** Genotropin; Humatrope; Norditropin; Nutropin; Omnitrope; Protropin†; Saizen; Serostim; Tev-Tropin; Zorbtive; ***Venez.:*** Genotropin; Humatrope; Norditropin†; Saizen.

Lanreotide *(BAN, rINN)*

Angiopeptin; BIM-23014; BN-52030; DC-13-116; Lanreotid; Lanreotida; Lanréotide; Lanreotidi; Lanreotidum. 3-(2-Naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide cyclic (2→7)-disulfide.

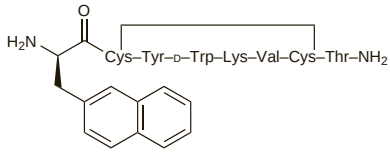
Ланреотид

$C_{54}H_{69}N_{11}O_{10}S_2$ = 1096.3.

CAS — 108736-35-2.

ATC — H01CB03.

ATC Vet — QH01CB03.



Lanreotide Acetate *(BANM, USAN, rINNM)*

Acetato de lanreotida; BIM-23014C; Lanréotide, Acétate de; Lanreotidi Acetas.

Ланреотида Ацетат

$C_{54}H_{69}N_{11}O_{10}S_2.x(C_2H_4O_2)$.

CAS — 127984-74-1.

ATC — H01CB03.

ATC Vet — QH01CB03.

Adverse Effects and Precautions

As for Octreotide Acetate, p.1803.

Interactions

As for Octreotide Acetate, p.1804.

Pharmacokinetics

After intravenous injection lanreotide has a terminal half-life of about 2.5 hours. Lanreotide is available as injectable depot preparations, and after subcutaneous or intramuscular use of these an initial rapid liberation of the drug is followed by more prolonged release with an apparent half-life of about 5 to 30 days. The absolute bioavailability is stated to range from about 50 to 80%, depending on the product.

Uses and Administration

Lanreotide is a somatostatin analogue with similar properties to those of octreotide (p.1804). It is given, as a long-acting depot injection, in the treatment of acromegaly (p.1798) and thyrotrophic adenoma, as well as in the symptomatic management of carcinoid syndrome (p.643).

Lanreotide is given as the acetate, but doses are usually expressed in terms of the base. The usual starting dose is equivalent to lanreotide 30 mg by intramuscular depot injection every 14 days. In acromegaly and carcinoid syndrome, this may be increased if necessary to 30 mg every 7 to 10 days; in thyrotrophic adenoma it may be increased to 30 mg every 10 days. An alternative preparation for acromegaly and carcinoid syndrome, given by deep subcutaneous injection every 28 days, delivers doses equivalent to 60, 90, or 120 mg of lanreotide. In patients with acromegaly who respond to treatment, lanreotide may be gradually reduced to maintenance doses of 120 mg given at intervals of up to 56 days. In those who are not adequately controlled, a maximum dose of 120 mg once every 28 days may be used.

Lanreotide has been tried for the prevention of restenosis in coronary blood vessels following angioplasty (see Reperfusion and Revascularisation Procedures, p.1181).

◊ References.

1. Wymenga ANM, *et al.* Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J Clin Oncol* 1999; **17:** 1111–17.
2. Kuhn JM, *et al.* Evaluation of the treatment of thyrotropin-secreting pituitary adenomas with a slow release formulation of the somatostatin analog lanreotide. *J Clin Endocrinol Metab* 2000; **85:** 1487–91.
3. Ayuk J, *et al.* Long-term safety and efficacy of depot long-acting somatostatin analogs for the treatment of acromegaly. *J Clin Endocrinol Metab* 2002; **87:** 4142–6.
4. Caron P, *et al.* One-year follow-up of patients with acromegaly treated with fixed or titrated doses of lanreotide Autogel. *Clin Endocrinol (Oxf)* 2004; **60:** 734–40.
5. Ruszniewski P, *et al.* Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology* 2004; **80:** 244–51.
6. Freda PU, *et al.* Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab* 2005; **90:** 4465–73.
7. Croxtall JD, Scott LJ. Lanreotide Autogel : a review of its use in the management of acromegaly. *Drugs* 2008; **68:** 711–23.

Administration in hepatic and renal impairment. The clearance of lanreotide, given by intravenous bolus, was significantly reduced in patients with severe chronic renal impairment requiring haemodialysis.[1] However, the authors of this study suggested that considering the wide therapeutic window of lanreotide, depot formulations may be given at the usual initial dose, with further doses adjusted according to response. Clearance of lanreotide was only slightly reduced in patients with moderate to severe hepatic impairment (Child-Pugh category B and C).[2] The UK licensed product information for one depot formulation (*Somatuline Autogel; Ipsen, UK*) given every 28 days recommends that dose adjustment is not necessary in renal or hepatic impairment. Another preparation (*Somatuline LA; Ipsen, UK*) usually given every 14 days suggests that renal and hepatic function should be monitored and the dosage interval adjusted as needed.

1. Barbanoj M, *et al.* Pharmacokinetics of the somatostatin analog lanreotide in patients with severe chronic renal insufficiency. *Clin Pharmacol Ther* 1999; **66:** 485–91.
2. Tomlinson B, *et al.* Pharmacokinetic profile of the somatostatin analogue lanreotide in individuals with chronic hepatic insufficiency. *Clin Pharmacokinet* 2006; **45:** 1003–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Somatuline; ***Austral.:*** Somatuline; ***Austria:*** Somatuline; ***Belg.:*** Somatuline; ***Braz.:*** Somatuline†; ***Cz.:*** Somatuline; ***Denm.:*** Ipstyl; ***Fin.:*** Somatuline; ***Fr.:*** Somatuline; ***Ger.:*** Somatuline; ***Gr.:*** Somatuline; ***Hong Kong:*** Somatuline; ***Hung.:*** Somatuline; ***Irl.:*** Somatuline; ***Israel:*** Somatuline; ***Ital.:*** Ipstyl; ***Neth.:*** Somatuline; ***Norw.:*** Ipstyl; ***Pol.:*** Somatuline; ***Port.:*** Somatulina; ***Rus.:*** Somatuline (Соматулин); ***Singapore:*** Somatuline; ***Spain:*** Somatulina; ***Swed.:*** Somatuline; ***Switz.:*** Somatuline; ***UK:*** Somatuline; ***USA:*** Somatuline.

Octreotide Acetate *(BANM, USAN, rINNM)*

Acetato de octreotida; Octréotide, Acétate d'; Octreotidi Acetas; SMS-201-995 (octreotide). 2-(D-Phenylalanyl-L-cystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-cystyl)-(2*R*,3*R*)-butane-1,3-diol acetate; D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7) disulphide acetate.

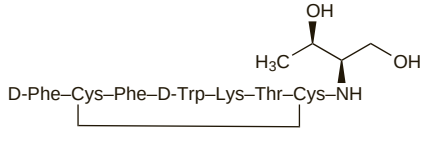
Октреотида Ацетат

$C_{49}H_{66}N_{10}O_{10}S_2.xC_2H_4O_2$ = 1019.2 (octreotide).

CAS — 83150-76-9 (octreotide); 79517-01-4 (octreotide acetate).

ATC — H01CB02.

ATC Vet — QH01CB02.



(octreotide)

Incompatibility. Apparent loss of insulin has been reported from a total parenteral nutrient solution containing octreotide; there may be an incompatibility.[1] Also the manufacturers had suggested that octreotide might be adsorbed onto plastics. However, a solution containing octreotide 200 micrograms/mL as the acetate was reported to be stable at 5° or −20° for up to 60 days when stored in polypropylene syringes.[2]

1. Rosen GH. Potential incompatibility of insulin and octreotide in total parenteral nutrient solutions. *Am J Hosp Pharm* 1989; **46:** 1128.
2. Ripley RG, *et al.* Stability of octreotide acetate in polypropylene syringes at 5 and −20°C. *Am J Health-Syst Pharm* 1995; **52:** 1910–11.

Adverse Effects and Precautions

There may be a transient local reaction at the site of injection of octreotide. Systemic adverse effects are mainly gastrointestinal and may include anorexia, nausea, vomiting, diarrhoea and steatorrhoea, abdominal discomfort, and flatulence. Use between meals or at bedtime may reduce these gastrointestinal effects. Hypersensitivity reactions and hair loss have been reported rarely.

Gallstones may develop on long-term therapy; there have been isolated reports of hepatic dysfunction and of biliary colic associated with drug withdrawal. Checks should be made for gallstones before prolonged therapy and at 6- to 12-month intervals during treatment. There have also been isolated reports of pancreatitis and of hepatic dysfunction without cholestasis. Hypoglycaemia may occur, especially in patients with insulinomas, but there is also a risk of hyperglycaemia or impaired glucose tolerance. Thyroid function should be monitored during octreotide therapy because of the possibility of hypothyroidism. Pituitary tumours that secrete growth hormone can expand during treatment, causing serious complications; patients should be monitored for signs of tumour expansion, such as visual field defects. Cardiac rhythm should be monitored during intravenous use of octreotide. Doses may need to be adjusted in patients with end-stage renal failure, in whom the clearance of octreotide is reduced.

Effects on the biliary tract. Octreotide has an inhibitory effect on gallbladder motility and bile secretion, accounting for the development of gallstones and biliary colic.[1-5]

1. Redfern JS, Fortuner WJ. Octreotide-associated biliary tract dysfunction and gallstone formation: pathophysiology and management. *Am J Gastroenterol* 1995; **90:** 1042–52.
2. Tauber JP, *et al.* The impact of continuous subcutaneous infusion of octreotide on gallstone formation in acromegalic patients. *J Clin Endocrinol Metab* 1995; **80:** 3262–6.
3. Hussaini SH, *et al.* Roles of gall bladder emptying and intestinal transit in the pathogenesis of octreotide induced gall bladder stones. *Gut* 1996; **38:** 775–83.
4. Trendle MC, *et al.* Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. *Cancer* 1997; **79:** 830–4.
5. Moschetta A, *et al.* Severe impairment of postprandial cholecystokinin release and gall-bladder emptying and high risk of gallstone formation in acromegalic patients during Sandostatin LAR. *Aliment Pharmacol Ther* 2001; **15:** 181–5.

Effects on carbohydrate metabolism. Changes in glucose tolerance may occur in patients with acromegaly who are treated with somatostatin analogues. In a study[1] of 90 patients treated with octreotide for 6 months, impaired glucose tolerance or frank diabetes developed in half of the 55 who initially had normal glucose tolerance. There was initial impaired glucose tolerance in 24 patients, which deteriorated in 4, remained stable in 10, and normalised in 10. Of the 11 patients who were diabetic before octreotide treatment, 8 remained diabetic but 1 improved to having impaired glucose tolerance and 2 to being normal. A later study[2] of 24 patients treated with either octreotide or lanreotide also found that glucose tolerance could remain stable, deteriorate, or improve. Overall, however, there was an improvement in insulin resistance but an impairment of insulin secretion, and a deterioration in glucose homoeostasis in nondiabetic patients.

There has been a report of deterioration in glucose tolerance leading to death from diabetic ketoacidosis when octreotide treatment was stopped in a patient with acromegaly and insulin-resistant diabetes mellitus.[3]

See also Diabetes Mellitus and Hyperinsulinism under Uses and Administration, below.

1. Koop BL, *et al.* Effect of octreotide on glucose tolerance in acromegaly. *Eur J Endocrinol* 1994; **130:** 581–6.
2. Baldelli R, *et al.* Glucose homeostasis in acromegaly: effects of long-acting somatostatin analogues treatment. *Clin Endocrinol (Oxf)* 2003; **59:** 492–9.
3. Abrahamson MJ. Death from diabetic ketoacidosis after cessation of octreotide in acromegaly. *Lancet* 1990; **336:** 318–19.