

phosphataemia and dyspnoea have been associated with high-dose intravenous bolus therapy.² Mecasermin is now given by subcutaneous injection (see Uses and Administration, below).

1. Malozowski S, Stadel B. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; **121**: 549.
2. Usala A-L. Risks and benefits of insulin-like growth factor. *Ann Intern Med* 1994; **121**: 550.

Pharmacokinetics

After subcutaneous injection, mecasermin has a bioavailability of almost 100% in healthy subjects. In the circulation it is bound to 6 binding proteins, with more than 80% bound to binding protein 3 (IGFBP-3). However, IGFBP-3 is greatly reduced in patients with severe primary IGF-I deficiency, such that there is an increase in the clearance of mecasermin. Mecasermin is metabolised in the liver and the kidney, and has a terminal half-life of about 6 hours in children with severe primary IGF-I deficiency.

After subcutaneous injection of mecasermin rinfabate in children with severe primary IGF-I deficiency, the half-life of free IGF-I is prolonged to about 13 hours and IGFBP-3 has a half-life of about 54 hours.

Uses and Administration

The somatomedins are a group of polypeptide hormones, some of which are involved in mediating the effects of growth hormone in the body. Insulin-like growth factor I (IGF-I) is believed to be responsible for many of the anabolic effects of growth hormone. It is secreted primarily by the liver, regulated principally by growth hormone and insulin secretion; IGF-I may also be secreted in other tissues, where it may exert local hormonal (paracrine) effects. In the circulation, IGF-I is almost completely protein bound; 6 binding proteins have been identified and production of some of these is also under the control of growth hormone. In addition to its anabolic effects IGF-I, which is structurally related to insulin, also has potent hypoglycaemic properties.

IGF-I is available as mecasermin, a product of recombinant DNA technology. It is used in the treatment of growth failure in children with severe primary IGF-I deficiency (such as Laron-type dwarfism, in which an abnormality of the growth hormone receptor results in an inability to secrete endogenous IGF-I—see Growth Retardation, below). It may also be used in children with growth hormone gene deletion who have developed neutralising antibodies to growth hormone. However, it is not recommended for children less than 2 years of age because of a lack of data. The starting dose of mecasermin is 40 to 80 micrograms/kg twice daily by subcutaneous injection. After 1 week, if this dose is tolerated, it may be increased by 40 micrograms/kg per dose to a maximum of 120 micrograms/kg twice daily. Mecasermin should be given within 20 minutes before or after food, to minimise hypoglycaemia. The dose should be reduced if hypoglycaemia occurs with recommended doses despite adequate food intake. If the patient is unable to eat for any reason, the dose of mecasermin should be withheld.

Mecasermin rinfabate is a recombinant protein complex of IGF-I and its most abundant binding protein, insulin-like growth factor binding protein-3 (IGFBP-3). It is under investigation in the management of amyotrophic lateral sclerosis and myotonic muscular dystrophy.

IGF-II (IGF-2) is thought to play an important role in fetal growth, although its function in adults is uncertain. It is closely related in structure to IGF-I, but is not under the control of growth hormone.

♦ General reviews.

1. Laron Z. Somatomedin-I (insulin-like growth factor-I) in clinical use: facts and potential. *Drugs* 1993; **45**: 1–8.
2. Bondy CA, et al. Clinical uses of insulin-like growth factor I. *Ann Intern Med* 1994; **124**: 593–601.
3. Le Roith D. Insulin-like growth factors. *N Engl J Med* 1997; **336**: 633–40.
4. Laron Z. Insulin-like growth factor I (IGF-1): a growth hormone. *Mol Pathol* 2001; **54**: 311–16.
5. Kemp SF, et al. Efficacy and safety of mecasermin rinfabate. *Expert Opin Biol Ther* 2006; **6**: 533–8.

Diabetes mellitus. Patients with type 1 diabetes mellitus (p.431) have low circulating levels of insulin-like growth factor I (IGF-I), and there has been considerable interest in the therapeutic potential of mecasermin in these patients.¹ Randomised studies^{2–3} have found that mecasermin 40 micrograms/kg once or twice daily by subcutaneous injection improves metabolic control in the short term when added to insulin therapy. Insulin doses can also be reduced in some patients.³ However, the role of IGF-I in the development of diabetic complications is unclear and there has been some concern about its proliferative effect in diabetic retinopathy.¹ Optic disc swelling and worsening of retinopathy have been reported with higher doses of mecasermin.³ Mecasermin rinfabate is being studied in an attempt to limit adverse effects such as oedema, jaw pain, headache, Bells' palsy, and retinal oedema.⁴

Mecasermin has also been reported to improve insulin sensitivity and to lower concentrations of insulin, glucose, and C-peptide in patients with syndromes of severe insulin resistance or type 2 diabetes mellitus.¹

1. Thraikill KM. Insulin-like growth factor-I in diabetes mellitus: its physiology, metabolic effects, and potential clinical utility. *Diabetes Technol Ther* 2000; **2**: 69–80.
2. Acerini CL, et al. Randomised placebo-controlled trial of human recombinant insulin-like growth factor I plus intensive insulin therapy in adolescents with insulin-dependent diabetes mellitus. *Lancet* 1997; **350**: 1199–1204.
3. Thraikill KM, et al. Cotherapy with recombinant human insulin-like growth factor I and insulin improves glycaemic control in type 1 diabetes. *Diabetes Care* 1999; **22**: 585–92.
4. Clemmons DR, et al. The combination of insulin-like growth factor I and insulin-like growth factor-binding protein-3 reduces insulin requirements in insulin-dependent type 1 diabetes: evidence for in vivo biological activity. *J Clin Endocrinol Metab* 2000; **85**: 1518–24.

Growth retardation. Mecasermin is used in the treatment of Laron-type dwarfism (growth hormone resistance), a form of growth retardation (p.1798). Doses of 150 to 240 micrograms/kg daily, given subcutaneously, have stimulated linear growth and normalised biochemical abnormalities in these patients.¹ During long-term use, growth hormone and insulin are persistently suppressed, preventing hypoglycaemia and stabilising blood-glucose concentrations. There is also an increase in the production of the insulin-like growth factor binding protein-3, which prolongs the half-life of mecasermin so that a progressive dose reduction is needed to avoid overdosage and adverse effects.²

1. Laron Z. The essential role of IGF-I: lessons from the long-term study and treatment of children and adults with Laron syndrome. *J Clin Endocrinol Metab* 1999; **84**: 4397–4404.
2. Laron Z. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958–2003. *J Clin Endocrinol Metab* 2004; **89**: 1031–44.

Motor neurone disease. Mecasermin is under investigation for the management of amyotrophic lateral sclerosis, a form of motor neurone disease (p.2380). Mecasermin may have modest benefits but there is not enough available evidence to assess conclusively.¹

1. Mitchell JD, et al. Recombinant human insulin-like growth factor I (rhIGF-I) for amyotrophic lateral sclerosis/motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 21/08/08).

Osteoporosis. Mecasermin¹ and mecasermin rinfabate² have been investigated as stimulants of bone formation in osteoporosis (p.1084). Some beneficial effects on bone density have been reported.

1. Grinspoon S, et al. Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. *J Clin Endocrinol Metab* 2002; **87**: 2883–91.
2. Boonen S, et al. Musculoskeletal effects of the recombinant human IGF-1/IGF binding protein-3 complex in osteoporotic patients with proximal femoral fracture: a double-blind, placebo-controlled pilot study. *J Clin Endocrinol Metab* 2002; **87**: 1593–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz: Increlex; **Fr:** Increlex; **UK:** Increlex; **USA:** Increlex; [Iplex].

Somatorelin (rINN) ⊗

GHRF; GHRH; GRF; GRF-44; Growth Hormone-releasing Factor (Human); Growth Hormone-releasing Hormone; Somatoliberin; Somatolibin; Somatolibin; Somatolibin; Somatolibin.

Соматорелин

$C_{215}H_{358}N_{72}O_{66}S = 5039.7$.

CAS — 83930-13-6.

ATC — V04CD05.

ATC Vet — QV04CD05.

Sermorelin Acetate (BANM, USAN, rINN) ⊗

Acetato de sermorelina; GRF(1–29)NH₂ (sermorelin); Growth Hormone-releasing Factor (Human)-(1–29)-peptide Amide (sermorelin); Sermoreline, Acétate de; Sermorelini Acetas. Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH₂ acetate hydrate.

Серморелина Ацетат

$C_{149}H_{246}N_{44}O_{42}S \cdot xC_2H_4O_2 \cdot yH_2O = 3357.9$ (sermorelin).

CAS — 86168-78-7 (sermorelin); 114466-38-5 (sermorelin acetate).

ATC — H01AC04; V04CD03.

ATC Vet — QH01AC04; QV04CD03.

Adverse Effects and Precautions

Facial flushing and pain at the injection site may occur after injection of sermorelin acetate. Headache, nausea and vomiting, dysgeusia, and tightness in the chest have also been reported. Antibodies to somatorelin may develop on repeated use.

Sermorelin should be used with care in patients with epilepsy. Uncontrolled hypothyroidism, obesity, hyperglycaemia, or elevated plasma fatty acids may impair response to sermorelin. Sermorelin should not be used to treat growth retardation in children whose growth hormone response to stimulation tests is inadequate. Treatment should cease once the epiphyses have closed.

Interactions

Drugs that affect the secretion of growth hormone may interfere with the diagnostic efficacy of somatorelin or sermorelin; these include growth hormone itself, somatostatin, insulin, corticosteroids, and cyclo-oxygenase inhibitors such as aspirin and indometacin. Growth hormone concentrations may be raised by clonidine and levodopa. The response to somatorelin or sermorelin may also be reduced by antimuscarinic drugs such as atropine, and by antithyroid drugs such as propylthiouracil.

Uses and Administration

Somatorelin is a peptide, secreted by the hypothalamus, that promotes the release of growth hormone from the anterior pituitary. It exists as 44-, 40-, and 37-amino acid peptides; the 44-amino acid form may possibly be converted to the smaller forms but all are reported to be active, the activity residing in the first 29 amino acid residues. Sermorelin is a synthetic peptide corresponding to the 1–29 amino acid sequence of somatorelin.

Sermorelin acetate is used for the diagnosis of growth hormone deficiency. The usual dose is the equivalent of sermorelin 1 microgram/kg by intravenous injection in the morning after an overnight fast. A normal response to sermorelin indicates that the somatotrophs are functional, but does not exclude growth hormone deficiency due to hypothalamic dysfunction; to establish a diagnosis it must be used with other tests. Somatorelin acetate is used similarly.

Sermorelin has also been used for the treatment of growth hormone deficiency in children; doses equivalent to 30 micrograms/kg, as the acetate, may be given once daily at bedtime by subcutaneous injection.

Sermorelin has also been tried as an adjunct to gonadotrophin therapy in the induction of ovulation and has been investigated in the treatment of HIV-associated wasting.

Diagnostic use. Somatorelin (in its 40- or 44-amino acid forms) has been used in the assessment of growth hormone deficiency.^{1–3} It has usually been given as a single intravenous injection in doses of 1 microgram/kg or total doses of up to 200 micrograms. Subsequent normal or exaggerated increases in serum-growth hormone concentrations have occurred in healthy subjects,^{1,2} and in patients with hypothalamic tumours³ or acromegaly,² but not in patients with hypopituitarism.² A synthetic 29-amino-acid sequence of somatorelin, sermorelin acetate is now available for the diagnosis of growth hormone deficiency. However, it has been suggested that the test is not useful for screening as it does not test the hypothalamic-pituitary axis, and that it should not be used in routine clinical practice.⁴ The use of

sermorelin with the synthetic hexapeptide growth-hormone-releasing peptide-6 has also been reported.^{5,6}

1. Thorne MO, *et al.* Human pancreatic growth-hormone-releasing factor selectively stimulates growth-hormone secretion in man. *Lancet* 1983; **i**: 24–8. Correction. *ibid.*; 256.
2. Wood SM, *et al.* Abnormalities of growth hormone release in response to human pancreatic growth hormone releasing factor (GRF (1-44)) in acromegaly and hypopituitarism. *BMJ* 1983; **286**: 1687–91.
3. Grossman A, *et al.* Growth-hormone-releasing factor in growth hormone deficiency: demonstration of a hypothalamic defect in growth hormone release. *Lancet* 1983; **ii**: 137–8.
4. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72**: 362–8.
5. Popovic V, *et al.* GH-releasing hormone and GH-releasing peptide-6 for diagnostic testing in GH-deficient adults. *Lancet* 2000; **356**: 1137–42.
6. Leal A, *et al.* A single growth hormone (GH) determination is sufficient for the diagnosis of GH-deficiency in adult patients using the growth hormone releasing hormone plus growth hormone releasing peptide-6 test. *Clin Endocrinol (Oxf)* 2002; **57**: 377–84.

Growth retardation. Sermorelin has been studied in children with growth hormone deficiency (p.1798), usually given in doses of 30 micrograms/kg subcutaneously daily. Although there have been reports of improved growth rates,^{1–3} there are limited data directly comparing these with growth hormone. One large study⁴ 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.

1. Neyzi O, *et al.* Growth response to growth hormone-releasing hormone(1–29)-NH compared with growth hormone. *Acta Paediatr Suppl* 1993; **388**: 16–21.
2. Lanes R, *et al.* Long term therapy with a single daily subcutaneous dose of growth hormone releasing hormone (1-29) in prepubertal growth hormone deficient children. *J Pediatr Endocrinol* 1994; **7**: 303–8.
3. Ogilvy-Stuart AL, *et al.* Treatment of radiation-induced growth hormone deficiency with growth hormone-releasing hormone. *Clin Endocrinol (Oxf)* 1997; **46**: 571–8.
4. Thorne 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.

Lipodystrophy. In a placebo-controlled study¹ of 31 men with HIV-related lipodystrophy, insulin-like growth factor I (IGF-I) concentrations and body composition measures were improved in those given sermorelin 1 mg twice daily subcutaneously for 12 weeks.

1. Koutkia P, *et al.* Growth hormone-releasing hormone in HIV-infected men with lipodystrophy: a randomized controlled trial. *JAMA* 2004; **292**: 210–18.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Geref; **Belg.:** GHRH; **Denm.:** Somatrelf; **Fin.:** Geref; **Fr.:** Stimu-GH; **Ger.:** GHRH; **Gr.:** Geref; **Hong Kong:** Geref; **Irl.:** Geref; **Ital.:** Geref; **GHRH;** **Neth.:** GHRH; **Norw.:** Geref; **Port.:** Geref; **Spain:** Geref; **Swed.:** Geref; **Switz.:** Geref; **GHRH;** **UK:** Geref; **GHRH;** **USA:** Geref.

Somatostatin (BAN, rINN)

GH-RIF; GHRH; Growth-hormone-release-inhibiting Hormone; Somatostatiini; Somatostatina; Somatostatinas; Somatostatine; Somatostatinum; Somatotrophin-release-inhibiting Factor; Szomatostatin. Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys cyclic (3→14) disulphide.

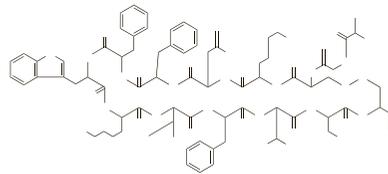
Соматостатин

$C_{76}H_{104}N_{18}O_{19}S_2 = 1637.9$.

CAS — 38916-34-6.

ATC — H01CB01.

ATC Vet — QH01CB01.



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

Ph. Eur. 6.2 (Somatostatin). A cyclic tetradecapeptide having the structure of the hypothalamic hormone that inhibits the release of human growth hormone. It is produced by chemical synthesis and contains not more than 15% w/w of acetic acid. A white amorphous powder. Freely soluble in water and in acetic acid; practically insoluble in dichloromethane. Store in airtight containers at a temperature of 2° to 8°. Protect from light and moisture.

Somatostatin Acetate (BANM, rINNM)

Acetate de somatostatina; Somatostatiinasettaati; Somatostatini Asetat; Somatostatiniacetat; Somatostatine, Acétate de; Somatostatini Acetas.

Соматостатина Ацетат

ATC — H01CB01.

ATC Vet — QH01CB01.

Adverse Effects and Precautions

Abdominal discomfort, flushing, nausea, and bradycardia have been associated with too rapid infusion. Because of the short half-life of somatostatin adverse effects are generally transitory on stopping or reducing the infusion. Giving with parenteral nutrition has been suggested because of the inhibitory effects of somatostatin on intestinal absorption; blood glucose should be monitored since somatostatin may interfere with the secretion of insulin and glucagon.

Effects on the kidneys. Somatostatin has been reported to have an inhibitory effect on renal function^{1,2} and severe water retention and hyponatraemia have been reported.³

1. Walker BJ, *et al.* Somatostatin and water excretion. *Lancet* 1983; **i**: 1101–2.
2. Vora JP, *et al.* Effect of somatostatin on renal function. *BMJ* 1986; **292**: 1701–2.
3. Halma C, *et al.* Life-threatening water intoxication during somatostatin therapy. *Ann Intern Med* 1987; **107**: 518–20.

Uses and Administration

Somatostatin is a polypeptide obtained from the hypothalamus or by synthesis. The naturally occurring form has a cyclic structure. Although somatostatin derived from the hypothalamus is a 14-amino-acid peptide, a longer, 28-amino-acid form also exists in some tissues. Somatostatin inhibits the release of growth hormone (p.1799) from the anterior pituitary. It also inhibits the release of thyrotrophin (p.2177) and corticotrophin (p.1523) from the pituitary, glucagon and insulin from the pancreas, and appears to have a role in the regulation of duodenal and gastric secretions. In the CNS it appears to play a role in the perception of pain. It has been tried in a variety of disorders such as upper gastrointestinal haemorrhage including variceal haemorrhage (see under Monoethanolamine, p.2346), insu-

lin resistance, and the management of hormone-secreting tumours and other hypersecretory disorders. However, it has a very short duration of action and several analogues of somatostatin have been produced in an attempt to prolong its activity as well as making its inhibitory effects more specific. Octreotide (p.1803) and lanreotide (p.1803) are such analogues.

Somatostatin is usually given as the acetate. In the treatment of gastrointestinal haemorrhage, such as acute bleeding from oesophageal varices, somatostatin acetate equivalent to somatostatin 250 micrograms has been given by intravenous bolus over 3 to 5 minutes, followed by a continuous infusion of 250 micrograms/hour (about 3.5 micrograms/kg per hour) until the bleeding has stopped, which is usually within 12 to 24 hours. The infusion may then be continued for a further 48 to 72 hours to prevent recurrent bleeding. In some cases, the infusion may be continued to a maximum of 120 hours.

Malignant neoplasms. Somatostatin given with melatonin, bromocriptine, and a solution of retinoids (the Di Bella regimen) was ineffective in the treatment of advanced malignancies (see Malignant Neoplasms, under Uses and Administration of Octreotide, p.1806).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Stilamin†; **Austria:** Somatin; **Somatalan;** **Belg.:** Modustatine†; **Braz.:** Stilamin†; **Canada:** Stilamin; **Cz.:** Stilamin†; **Fr.:** Modustatine; **Ger.:** Aminopant†; **Gr.:** Atostan; **Eklivan;** **Sadolin;** **Somabion;** **Somargen;** **Somaritin;** **Somastin;** **Stilamin;** **Hong Kong:** Stilamin; **Hung.:** Somatin†; **Stilamin†;** **India:** Somastin; **Stilamin†;** **Indon.:** Stilamin; **Ital.:** Etaxene; **Ikestatina;** **Modustatina;** **Nastoren;** **Resumiride;** **Stilamin;** **Zecni†;** **Malaysia:** Stilamin; **Mex.:** Stilamin†; **Neth.:** Stilamin†; **Port.:** Stilamin†; **S.Afr.:** Stilamin; **Singapore:** Stilamin; **Spain:** Somiaton†; **Somonal;** **Switz.:** Stilamin; **Thai.:** Etaxene; **Stilamin;** **Turk.:** Somatosan; **Stilamin;** **Venez.:** Ikestatina; **Stilamin.**

Vapreotide (BAN, USAN, rINN)

BMV41606; RC-160; Vapreotida; Vapreotide; Vapreotidum. D-Phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-tryptophanamide cyclic (2→7)-disulfide.

Вап্রেотид

$C_{57}H_{70}N_{12}O_9S_2 = 1131.4$.

CAS — 103222-11-3.

ATC — H01CB04.

ATC Vet — QH01CB04.



Profile

Vapreotide is a somatostatin analogue similar to octreotide (p.1803). It is under investigation in the management of various disorders, including bleeding oesophageal varices, gastrointestinal and pancreatic fistulas, acromegaly, carcinoid tumours, and for the prevention of postoperative complications following pancreatic surgery.

References

1. Eriksson B, *et al.* The use of new somatostatin analogues, lanreotide and octastatin, in neuroendocrine gastro-intestinal tumours. *Digestion* 1996; **57** (suppl 1): 77–80.
2. Calès P, *et al.* Early administration of vapreotide for variceal bleeding in patients with cirrhosis. *N Engl J Med* 2001; **344**: 23–8.
3. Anonymous. Vapreotide: BMV 41606, RC 160, Sanvar. *Drugs R D* 2003; **4**: 326–30.