Drugs of the Future 2006, 31(5): 390-399

CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.05.997158

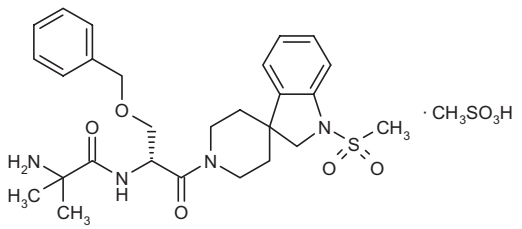
Ibutamoren Mesilate

Growth Hormone Secretagogue

Prop INNM; USAN

L-163191
MK-0677
MK-677
Crescendo®

2-Amino-*N*-[2-benzyloxy-1(*R*)-[1-(methanesulfonyl)spiro[indoline-3,4'-piperidin]-1'-ylcarbonyl]ethyl]isobutyramide methanesulfonate



$C_{28}H_{40}N_4O_8S_2$
Mol wt: 624.7714

CAS: 159752-10-0

CAS: 159633-92-8 (as monohydrochloride)

CAS: 159634-47-6 (as free base)

EN: 226508

Abstract

Growth hormone (GH) is a pleiotropic hormone that is released from the pituitary in a pulsatile manner to promote body growth and fat mobilization and inhibit glucose utilization. The hormone interacts with most tissues of the body and there are therefore numerous pathological endocrine and metabolic conditions that involve or are due to faulty GH secretion. Recombinant GH has been used to treat many of these conditions, but it must be administered by injection and is associated with a number of adverse events. Researchers have speculated that synthetic GH secretagogues (GHSs) may be more effective than recombinant GH in inducing physiological pulsatile GH secretion and have focused on identifying novel GHSs to be used clinically. One promising GHS is the orally active, nonpeptide spironindolinesulfonamide ibutamoren mesilate (MK-0677, L-163194). The agent has exhibited good oral activity and duration of action and was effective clinically for a number of GH-related indications. Ibutamoren is now in phase II development for the treatment of fibromyalgia, Alzheimer's disease and sarcopenia.

Synthesis

Ibutamoren can be synthesized by several related methods.

After sulfonylation of 1'-methyl-1,2-dihydrospiro[3*H*-indole-3,4'-piperidine] (I) with methanesulfonyl chloride, the resulting sulfonamide (II) is demethylated to (III) using 1-chloroethyl chloroformate (1-6). Subsequent coupling of the spiropiperidine (III) with *N*-Boc-*O*-benzyl-D-serine (IV) gives the amide (V). Acidic cleavage of the *N*-Boc protecting group of (V) to provide compound (VI), followed by coupling with *N*-Boc-2-aminoisobutyric acid (VII), gives the Boc-protected dipeptide amide (VIII), which is then deprotected under acidic conditions to give ibutamoren, which is finally isolated as the mesylate salt (1-9). Scheme 1.

The precursor spiropiperidine (III) can be synthesized by an alternative method. Isonipecotic acid (IX) is protected as the benzyloxycarbonyl derivative (X), followed by chlorination with oxalyl chloride, to give the acid chloride (XI). Selective reduction of (XI) to the aldehyde (XII) is then accomplished by hydrogenation in the presence of Pd/C, DIEA and thioanisole. Fischer indolization of (XII) with phenylhydrazine and trifluoroacetic acid leads to the spiroindolenine (XIII), which is reduced to the spiroindoline (XIV) using $NaBH_4$. After sulfonylation of (XIV) with methanesulfonyl chloride, the benzoyloxycarbonyl sulfonamide obtained (XV) is deprotected to (III) by catalytic hydrogenation over Pd/C (1, 3, 4, 6-10). Scheme 1.

In a more convergent strategy, the dipeptide derivative (XX) is prepared prior to coupling with the spiropiperidine (III). *N*-Boc-*O*-benzyl-D-serine (XVI) is protected as the corresponding allyl ester (XVII), which, after *N*-Boc group cleavage and coupling with *N*-Boc-2-aminioisobutyric acid (XVIII), gives the dipeptide derivative (XIX). Subsequent allyl ester cleavage using potassium 2-ethylhexanoate and palladium catalyst leads to (XX) (1, 3-5).

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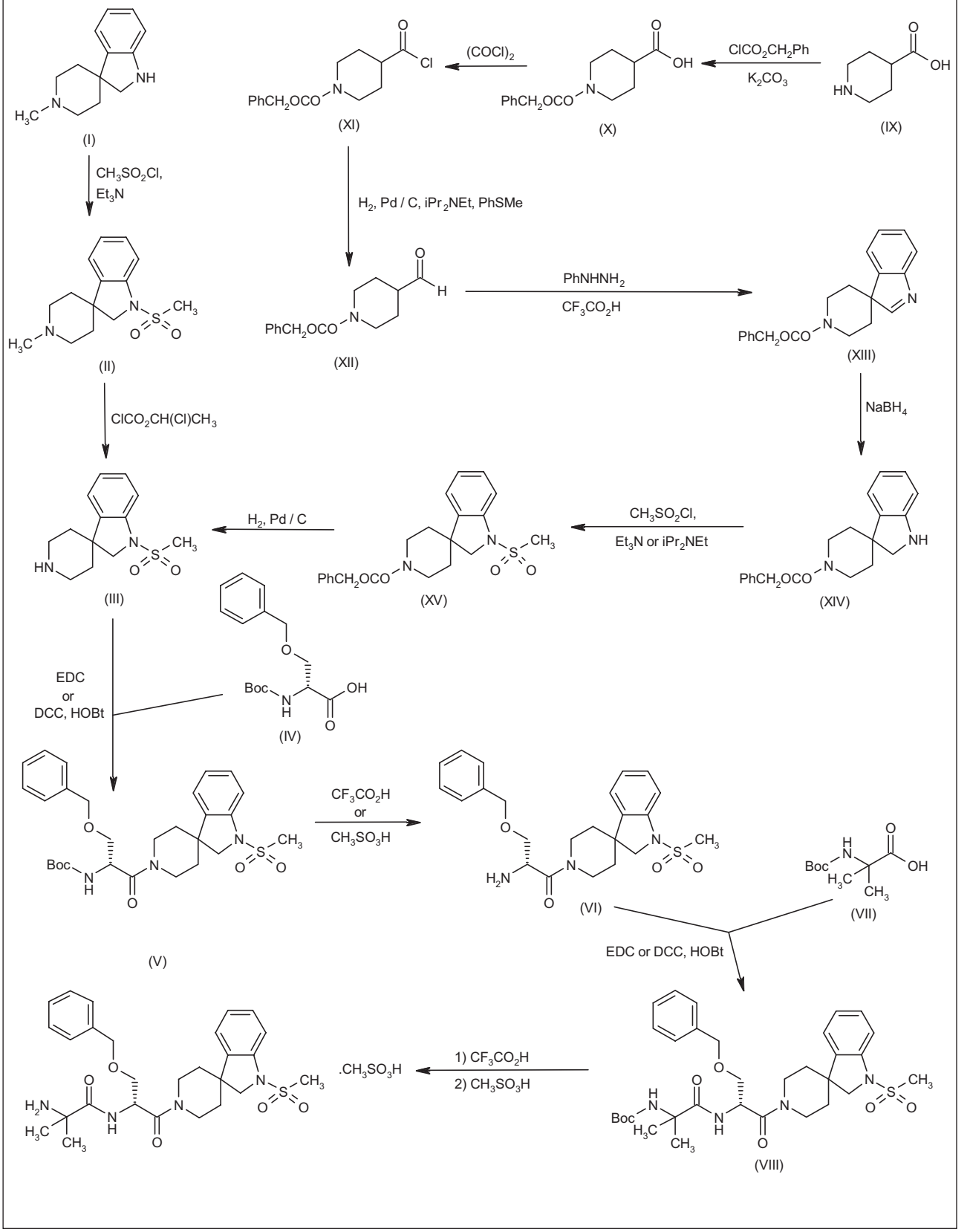
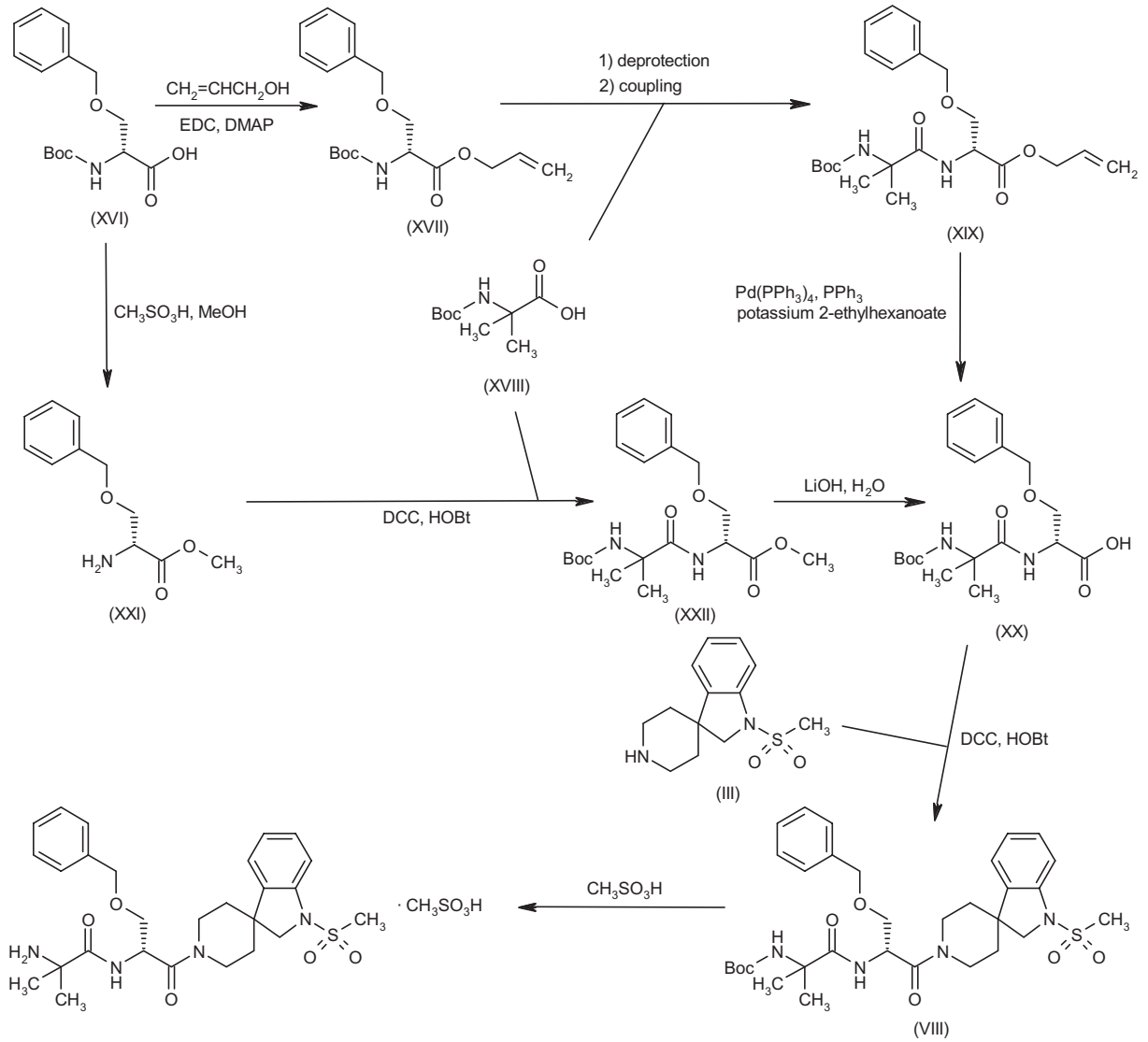
Scheme 1: Synthesis of Ibutamoren Mesilate



Scheme 2: Synthesis of Ibutamoren Mesilate



Alternatively, *N*-Boc-*O*-benzyl-D-serine (XVI) is deprotected and esterified to *O*-benzyl-D-serine methyl ester (XXI) using a methanolic solution of methanesulfonic acid. Subsequent coupling of (XXI) with (XVIII) yields the dipeptide ester (XXII), which is then hydrolyzed to (XX) by means of LiOH (10). The *N*-Boc-dipeptide (XX) is then coupled with the spiropiperidine (III) in the presence of DCC/HOBt to give the amide (VIII), which is finally converted to the title compound by treatment with methanesulfonic acid (1, 3-5, 10). Scheme 2.

Background

Growth hormone (GH) is a protein (191 amino acids; also known as somatotropin or somatropin) synthesized in the anterior lobe of the pituitary gland. It is secreted in a pulsatile fashion to promote body growth and fat mobilization and inhibit glucose utilization. It is a pleiotropic hormone which interacts with most tissues of the body and there are numerous pathological conditions that involve or are due to faulty GH secretion, such as dwarfism, aging-associated disorders, osteoporosis, obesity, gastrointestinal disorders, cachexia, eating disorders, fibromyalgia and sarcopenia, among others. The intricate interaction of growth hormone-releasing hormone (GHRH) and somatostatin tightly controls the pulsatile release of GH. GHRH is released from the hypothalamus to subsequently stimulate the synthesis and release of GH, while somatostatin, a tetradecapeptide found throughout the gastrointestinal tract in mucosal

endocrine cells, inhibits its release. Other neurotransmitters and neuropeptides are also suspected of being involved in the regulation of GH secretion. In addition to endogenous substances, the synthetic GH secretagogues (GHSs) can also potently stimulate GH secretion. This family of compounds, of which the prototype is GH-releasing peptide-6 (GHRP-6), were proposed as alternatives to GH, insulin-like growth factor I (IGF-I) and GHRH growth-promoting and anabolic therapies (11-17).

The synthetic GHSs most probably mimic actions of endogenous substances that modulate pulsatile GH secretion. Ghrelin was identified as an endogenous ligand for the orphan GHS receptor. Ghrelin and the gastrointestinal hormone motilin, which regulates gastrointestinal motility, are structurally similar and exert GH-releasing effects, and thus constitute a relatively novel gastrointestinal hormone family (18-20). GHSs exert their effects via specific G-protein-coupled receptors that are distinct from GHRH receptors. The two subtypes identified are the functional GHS receptor type Ia (GHS-RIa) and the nonspliced, nonfunctional mRNA variant. GHS-RIa is expressed mainly in the pituitary and hypothalamus but can also be detected at low levels in other brain regions (*e.g.*, ventral tegmental area, substantia nigra, nucleus tractus solitarius and hippocampus) and peripheral tissues including the heart, lung, pancreas, intestine, kidney and adipose tissue (21-23).

Researchers have speculated that GHSs may be more effective than recombinant GH in inducing physiological pulsatile GH secretion. Moreover, recombinant GH must be administered via injection and is associated with adverse events such as carpal tunnel syndrome. Thus, researchers have focused on identifying novel GHSs to be used clinically for the treatment of indications such as GH deficiency, eating disorders, fibromyalgia, cachexia, sarcopenia and other endocrine and metabolic disorders related to GH deficiency (24-26).

One promising GHS is the orally active, nonpeptide spironindolinesulfonamide ibutamoren mesilate (MK-0677, L-163194), which was synthesized using reverse pharmacology to discover leads for G-protein-coupled receptors. Ibutamoren enabled the identification of the GHS receptor and later its endogenous ligand ghrelin. Due to it good oral activity and duration of action, ibutamoren was selected for clinical development for the treatment of GH-related disorders (2, 21, 26-28).

Preclinical Pharmacology

Ibutamoren stimulated GH release from rat pituitary cells *in vitro* with an EC_{50} value of 1.3 ± 0.09 nM, which was lower than that of GHRP-6 (EC_{50} = 10.3 ± 1.9 nM) and close to that of GHRH (EC_{50} = 0.47 ± 0.09 nM). It appears that GHRP-6 and ibutamoren mediate pituitary GH release through the same receptor, since the effects of ibutamoren were blocked by a GHRP-6 antagonist; no increases in GH release were observed when the maximally effective concentrations of GHRP-6 and ibutamoren were combined and continuous exposure of pituitary cells to ibutamoren or GHRP-6 resulted in similar desensitization rates. In contrast to GHRP-6, when ibutamoren was combined with the maximally effective concentration of GHRH (10 nM), GH release was enhanced. Ibutamoren was shown to increase intracellular calcium (peak free cytosolic levels = 250-700 nM) in rat somatotrophs via activation of L-type Ca^{2+} channels and to activate protein kinase C (PKC). In addition, ibutamoren was specific for GH since IC_{50} values > 50 μM were obtained in assays for more than 50 receptors, including opiate, sigma, angiotensin II, bradykinin, 5-HT, muscarinic, neurokinin, galanin, vasopressin, benzodiazepine and endothelin receptors (2).

Ibutamoren was able to bind to membranes of BHK cells expressing human GHS-RIa (B_{max} = 2.0 ± 0.3 x 10^{-10} mol/mg protein) in a manner similar to adenosine (B_{max} = 2.6 ± 0.1 x 10^{-10} mol/mg protein); neither agent bound to membranes of nontransfected cells. Both ibutamoren and adenosine also increased intracellular calcium in transfected BHK cells (EC_{50} approximately 0.7 and 50 nM, respectively) (29).

Both ghrelin and ibutamoren were shown to displace [^{125}I]-ghrelin from the ghrelin receptor transiently expressed in COS-7 cells, with approximate IC_{50} values of 5-6.5 nM. Ibutamoren also activated several signal transduction systems (*e.g.*, calcium mobilization, inositol phosphate [IP] turnover, cAMP-responsive element [CRE]- and serum-responsive element [SRE]-controlled transcription and arrestin mobilization) with comparable potency (IC_{50} = 0.2-1.4 nM). Moreover, in contrast to GHRP-6 which was found to be a negative modulator of ghrelin in IP turnover assays, ibutamoren was a neutral modulator. Ghrelin and ibutmoren were also capable of inhibiting isoproterenol-induced lipolysis in rat adipocytes via the GHS-RIa (30, 31).

A study examining ibutamoren-induced *fos*-like immunoreactivity in conscious rats centrally and systemically injected with the agent *in vivo* showed selective neuronal activation of antidromically identified (*i.e.*, neuroendocrine) neurons within the arcuate nucleus. Further electrophysiological examination revealed that ibutamoren-induced excitation of these arcuate neuroendocrine neurons was attenuated by subsequent systemic somatostatin injection; the activity of neuroendocrine arcuate neurons unaffected by ibutamoren and non-neuroendocrine arcuate neurons was not altered by somatostatin injection. It was concluded that the population of neurons affected by ibutamoren and somatostatin was probably involved in GH release (32).

Ibutamoren effectively increased GH levels in dogs in a number of *in vivo* studies. Responses were observed even at low i.v. doses of 0.025 mg/kg. GH levels also increased following oral dosing, with responses first observed with a low dose of 0.125 mg/kg. Effects were dose-dependent and sustained for more than 2 h. The oral bioavailability of the agent was estimated to be more than 60%. The selectivity of oral ibutamoren was also examined. Following oral doses of 1 mg/kg, the AUC for GH over 8 h increased about 9-fold and cortisol AUC

about 2.4-fold, whereas aldosterone, luteinizing hormone (LH), prolactin and thyroxine levels were not significantly affected by treatment (2).

Similar results were obtained in another study where i.v. doses of 0.25, 0.5 and 1 mg/kg ibutamoren significantly increased total GH release (*i.e.*, AUC) and peak GH levels by 5.3-, 9.0- and 15.8-fold, respectively. An i.v. dose of 0.25 mg/kg resulted in a mean serum GH peak of 3.8 ± 0.7 ng/ml, which was significantly increased 20.4-fold as compared to controls. GH levels remained elevated up to 180 min postdosing. IGF-I levels were also increased by 25% at 360 min postdosing and cortisol levels increased 2.3-fold over baseline. While insulin and glucose levels tended to be higher and LH and prolactin levels lower in ibutamoren-treated dogs, the levels remained within the normal range. Following a single oral dose of 1 mg/kg, a mean GH peak of 27.6 ± 1.5 ng/kg was observed at 120 min and increases were sustained for up to 360 min postdosing. IGF-I levels were also significantly increased by 30% at 480 min postdosing and cortisol levels increased 2.4-fold (33).

The ibutamoren-induced increases in serum IGF-I were found to be mediated by the pituitary. Experiments carried out in dogs showed that mean peak serum GH levels were not increased following treatment with oral ibutamoren (1 mg/kg p.o.) 6 days after hypophysectomy. In contrast, ibutamoren induced increases in serum IGF-I levels prior to surgery and also in sham-treated dogs. Similar effects on cortisol were observed. The results suggest that ibutamoren does not directly stimulate increases in IGF-I or cortisol. Instead, these effects are mediated by the pituitary (34).

Chronic oral dosing with ibutamoren (0.25, 0.5 and 1 mg/kg/day for 14 days or on alternate days for 9 days) was shown to increase and maintain elevated serum IGF-I in beagles. GH secretion (*i.e.*, AUC) was increased 3.9-, 5.6- and 7.9-9.8-fold, respectively. Repeated dosing resulted in a 41-77% reduction in the GH response, suggesting IGF-I negative feedback on the GH axis. However, serum GH levels remained significantly above controls in the groups receiving 0.5 and 1 mg/kg. The increases in GH levels appeared to be related to amplified GH pulsatile profiles. On day 1 of treatment, serum IGF-I significantly increased by 480 min and repeated dosing resulted in an increase of up to 126%, which was sustained throughout the 14 days of treatment. On days 4-14, significant increases in IGF-I over pretreatment levels were observed over 24 h with daily but not alternate-day ibutamoren administration. An increase in cortisol secretion was observed on day 1 of the treatment period, but this response was attenuated with repeated daily dosing, indicating IGF-I-mediated negative feedback; the cortisol response did not decrease with repeated dosing on alternate days (35).

Examination of canine cerebrospinal fluid (CSF) following 15-day oral ibutamoren (5 mg/kg/day) or s.c. GH (0.1 IU/kg/day) administration *in vivo* revealed significant elevations in serum but not CSF GH and IGF-I levels. Treatment was also found to significantly increase body weight. There was no correlation between circulating and CSF GH and IGF-I levels in either control or treated dogs. Initial CSF IGF-I and GH levels were low, suggesting that there is a blood-brain barrier for circulating IGF-I and that the source of these hormones in the CSF is from the CNS (36).

Pharmacokinetics and Metabolism

Two sensitive and specific liquid chromatographic with atmospheric pressure chemical ionization tandem mass spectrometry assays were described that enable determination of ibutamoren in human plasma and its thermally labile hydroxylamine metabolite in both dog and human plasma. The assay for determination of ibutamoren levels was validated in human plasma using a concentration range of 0.1-100 ng/ml. The limit of quantification was 0.1 ng/ml and the precision was < 7% (coefficient of variation [CV]). The pharmacokinetics of ibutamoren were determined in humans using the assay following a single 5-mg oral dose of the drug. The second assay designed for determination of the ibutamoren metabolite was validated in both dog and human plasma using a concentration range of 0.5-500 ng/0.1 ml. The precision of this assay was < 10% (CV) over all concentrations except 0.5 ng/0.1 ml, for which it was 14% (CV) for human plasma. This assay was used to determine the pharmacokinetics of the ibutamoren metabolite in human and dogs following single doses of 5 mg and 0.5 mg/kg, respectively (37, 38).

The pharmacokinetics of ibutamoren were determined in rats and dogs. Oral administration of [^{3}H]-ibutamoren to rats resulted in urinary/biliary recoveries of radioactivity of 46% and 76% at 2 and 72 h, respectively, indicating rapid absorption. Bioavailability in rats was 6-22%. Oral administration to both rats and dogs resulted in nonlinear pharmacokinetics, such that AUC values increased disproportionately with dose. Plasma clearance following i.v. doses in rats was dose-independent and rapid (150-300 ml/min/kg). In contrast, plasma clearance was 10-fold lower in dogs (12-19 ml/min/kg) and was found to decrease between doses of 0.5 and 5 mg/kg. The terminal $t_{1/2}$ values for rats and dogs were about 2 and 5-6 h, respectively. At early time points following i.v. administration of [^{14}C]-ibutamoren to rats, the highest radioactivity was detected in adrenals, kidneys, lungs, heart and thyroid/parathyroid gland, and at later points, in the gastrointestinal tract and its contents. By 24 h, the majority of radioactivity was cleared from tissues. The desbenzylated derivative was the major metabolite found in rats and dogs, and ibutamoren was primarily eliminated by biliary excretion. In rats and dogs, 18% and 18%, respectively, of the radioactive i.v. dose was detected in urine and 74% and 61%, respectively, in feces (39).

Clinical Studies

The effects of 7 days of treatment with ibutamoren (5 and 25 mg p.o. at bedtime) on GH, IGF-I and cortisol pro-

files were examined in a randomized, double-blind, placebo-controlled, crossover trial in 9 healthy young men. Although GH secretion was similar in all groups, GH pulse frequency was increased with both ibutamoren doses as compared to placebo. Both doses of the agent dose-dependently increased IGF-I levels, which was positively correlated with GH pulse frequency. However, only the higher dose increased IGF-binding protein-3 (IGFBP-3). Mean 24-h levels of plasma total and free cortisol and urinary cortisol excretion were unchanged with treatment, indicating that ibutamoren has no effect on cortisol profiles. An advancement of the nocturnal nadir and morning elevation of cortisol was observed with treatment (40).

Another randomized, placebo-controlled, crossover study in 8 healthy volunteers subjected to diet-induced caloric restriction (18 kcal/kg/day for two 14-day periods with a 14-21-day washout between periods) examined the effects of ibutamoren (25 mg p.o. once daily for 7 days) on diet-reduced nitrogen wasting. Ibutamoren was generally well tolerated, with no significant adverse events reported. Treatment with the agent significantly improved overall nitrogen balance ($AUC_{days\ 8\text{-}14}$ nitrogen balance = +2.69 ± 5 g/day *vs.* –8.97 ± 5.26 g/day) and induced peak GH responses of 55.9 ± 31.7 and 22.6 ± 9.3 μg/l, respectively, after a single dose and 7 days of ibutamoren dosing; peak GH levels for the placebo group were approximately 9 and 7 μg/l, respectively. IGF-I levels, which decreased with caloric restriction, were significantly increased during the last 5 days of ibutamoren administration (264 ± 31 ng/ml *vs.* 188 ± 19 ng/ml on placebo) and IGFBP-3 levels also significantly increased as compared to placebo. No significant increases in IGFBP-2, serum cortisol or prolactin were observed with treatment. Results suggested that ibutamoren may be effective as a therapy for catabolic indications (41).

Ibutamoren (25 mg every morning) increased and sustained 24-h mean GH levels in healthy older subjects (60-81 years) participating in a 2-year, double-blind, placebo-controlled, crossover trial. A total of 65 male and female (on and off hormone replacement therapy [HRT]) subjects were included. Treatment with ibutamoren significantly increased 24-h mean GH and IGF-I levels at 6, 12 and 24 months as compared to placebo. The increase in IGF-I appeared to be greater in men compared to women and also in women on HRT compared to those off HRT. Mean levels of GH returned to baseline following crossover to placebo (42, 43).

Once-daily oral ibutamoren (2, 10 or 25 mg for up to 4 weeks) effectively stimulated the GH/IGF-I axis in healthy elderly male and female subjects entered in a randomized, double-blind, placebo-controlled trial. Serum GH increased dose-dependently after 2 weeks of ibutamoren treatment. The highest dose significantly increased 24-h mean GH levels by 97 ± 23%, which was due to an enhancement in pulsatile GH secretion. GH pulse height and interpulse nadir concentrations significantly increased, although the number of pulses was unaltered by treatment. The highest dose significantly increased mean serum IGF-I (219 ± 21 and 265 ± 29 μg/l at 2 and 4 weeks, respectively, *vs.* 141 ± 21 μg/l at baseline) to within the normal range for young adults. Fasting glucose and IGFBP-3 levels also significantly increased with ibutamoren. Serum cortisol levels were unchanged with treatment; prolactin levels increased 23%, although they remained within the normal range (44).

A double-blind, placebo-controlled, crossover trial in 8 young (18-30 years) and 6 older (65-71 years) healthy subjects with no sleep complaints examined the effects of ibutamoren (5 and 25 mg p.o. at bedtime) on sleep quality. Young subjects participated in three 7-day treatment periods (with a washout period of at least 14 days) and older subjects were involved in two 14-day treatment periods (with a 14-day washout period). A significant increase in the duration of stage IV sleep (about 50%) and REM sleep (> 20%) was observed in ibutamoren-treated young subjects compared to those on placebo; the higher dose also significantly decreased the frequency of deviations from normal sleep (8% *vs.* 42% on placebo). Older subjects treated with the agent experienced significant increases in REM sleep (nearly 50%) and REM latency, and significant decreases in deviations from normal sleep. Results suggest that ibutamoren may be effective in improving hyposomatotropism and loss in sleep quality associated with senescence (45).

The efficacy of ibutamoren (10 or 50 mg p.o. once daily for two 4-day treatment periods separated by at least 28 days) in stimulating the GH/IGF-I axis in severely GH-deficient adults (17-34 years; peak serum GH response to insulin-induced hypoglycemia = 1.2 ± 1.5 μg/l) was examined in a double-blind, rising-dose study in 9 subjects who had been treated with GH during childhood. Ibutamoren was generally well tolerated. Serum cortisol, prolactin and thyroid hormone levels were not significantly altered with treatment, although fasting and postprandial insulin and postprandial glucose levels significantly increased. Both doses of the agent significantly increased 24-h mean serum GH (79 ± 19% and 82 ± 29%, respectively) and IGF-I (52 ± 20% and 79 ± 9%, respectively) from baseline; serum IGFBP-3 significantly increased with both doses. Ibutamoren was more effective in inducing GH responses in those subjects with a greater GH/IGF-I deficiency at baseline (46).

The safety and tolerability of short-term ibutamoren (0.2 or 0.8 mg/kg p.o. on days 1-7 or 8-14 plus 0.8 mg/kg on day 15) treatment and its efficacy in stimulating the GH/IGF-I axis were examined in a multicenter, randomized, partially double-blind, placebo-controlled trial conducted in 18 prepubertal children with idiopathic GH deficiency (10.6 ± 0.8 years; maximum GH response for two different GH stimulation tests = 10 μg/l or less). Treatment was generally well tolerated and no serious adverse events were reported. Two cases of vomiting, 1 case of headache and 1 case of increased appetite were observed on the higher dose; all adverse events resolved spontaneously. Three cases of symptomatic, reversible increases (1.5-4-fold) in serum transaminases occurred in subjects treated for 8 days; levels decreased to normal at 1-4 weeks after the final ibutamoren dose. Treatment

with 0.8 mg/kg ibutamoren for 8 days resulted in a significant increase from baseline in serum GH (median = 3.8 μg/l), $AUC_{0\text{-}8\ h}$ for GH (4.3 μg.h/l), serum IGF-I (12 μg/l) and serum IGFBP-3 (0.4 μg/l). No changes in serum prolactin, glucose, triiodothyronine, thyroxine, thyrotropin, peak insulin or 24-h urinary free cortisol were observed even after 8 days of treatment with the higher dose (47).

A randomized, double-blind, placebo-controlled, parallel-group study in 24 obese (19-49 years; BMI > 30 kg/m^2; waist/hip ratios > 0.95) but generally healthy males examined the efficacy of ibutamoren (25 mg p.o. daily for 8 weeks). Significant increases in serum IGF-I (about 40%) and IGFBP-3 were observed with treatment. In addition, peak and AUC values for GH and prolactin were also significantly increased after the first dose; however, only GH levels remained significantly increased at 2 and 8 weeks. No significant increase was observed in serum or urinary cortisol concentrations at 2 and 8 weeks. A significant increase in fat-free mass was also observed in the ibutamoren-treated group, with significant changes in total and visceral fat reported; basal metabolic rate was significantly increased at 2 but not 8 weeks. Although fasting glucose and insulin levels were not significantly altered by treatment, an impairment in glucose homeostasis was noted in oral glucose tolerance tests at both 2 and 8 weeks (48). Treatment with the agent had no effect on lipoprotein(a), total cholesterol or low-density lipoprotein cholesterol (LDL-C) levels or on lipoprotein lipase activity in abdominal and gluteal s.c. adipose tissue. However, serum apoplipoprotein (apo) A-I, apoE, high-density lipoprotein cholesterol (HDL-C) and triglycerides were significantly increased at 2 but not 8 weeks of treatment; mean LDL particle diameter was significantly reduced at 2 weeks. After 8 weeks of therapy, the LDL-C/HDL-C ratio significantly decreased (49). Ibutamoren was generally well tolerated, with no serious adverse events reported. Five patients experienced ibutamoren-related adverse events which included transient gastritis at 4 weeks, transient mild sweating at 6 weeks, a transient increase in blood glucose of 10 mmol/l after 6 weeks which lasted 1 week, and 3 cases of asymptomatic, transient increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST). Treatment with the agent resulted in significant increases in bone formation markers starting at 2 weeks, including carboxy-terminal propeptide of type I procollagen (23%) and procollagen III peptide (28%); a significant 15% increase in osteocalcin was seen at 8 weeks. Bone resorption markers also significantly increased starting at 2 weeks, with levels of carboxy-terminal cross-linked telopeptide of type I collagen increasing by 26% at 8 weeks and urine hydroxyproline/creatinine and calcium/creatinine ratios at 8 weeks increasing by 23% and 46%, respectively. Significant increases were observed in serum IGFBP-5 (43-44%) after 2-8 weeks and IGFBP-4 (25%) at 2 weeks in the ibutamoren-treated group. There were no changes in plasma IL-6 (50).

The proportion of non-22K GH isoforms and 20K GH released following ibutamoren administration (25 mg p.o. daily for 8 weeks) was examined in a randomized, double-blind, placebo-controlled, parallel-group study including 12 obese (19-49 years; BMI > 30 kg/m^2; waist/hip ratios > 0.95) but generally healthy males. Analysis showed that, following the initial dose, the proportion of non-22K GH was significantly higher in peak but not non-peak total GH samples taken at 2 and 8 weeks. The proportion of 20K GH in samples at 2 h after the initial dose was lower than levels observed in samples taken after 2 and 8 weeks. It was concluded that these changes in non-22K GH isoforms would not significantly alter the clinical response to ibutamoren (51).

The tolerability and efficacy of ibutamoren (25 mg p.o. daily) and alendronate (10 mg p.o. daily) alone and in combination were determined in an 18-month multicenter, randomized, double-blind, placebo-controlled trial conducted in 292 postmenopausal osteoporotic women (64-85 years) with low femoral neck bone mineral density (BMD). Treatments were generally well tolerated, with only 25 patients discontinuing due to adverse events. GH-related adverse events such as fluid retention, weight gain, edema/swelling, abdominal distention, carpal tunnel syndrome, breast tenderness and elevations in glucose or prolactin were observed in groups receiving ibutamoren, although discontinuations due to these effects were infrequent. Treatment with ibutamoren alone or in combination significantly increased IGF-I (39% and 45%, respectively). Ibutamoren alone increased osteocalcin (22%) and urinary *N*-telopeptide cross-links (NTx; 41%) as compared to placebo. Combination treatment attenuated the indirect suppressive effects of alendronate on bone formation according to mean serum osteocalcin (–40% *vs.* –54%) and NTx (–52% *vs.* –61%) values. Treatment with alendronate alone resulted in progressive improvements in femoral neck, hip, lumbar spine and total-body BMD. Although combination treatment significantly enhanced the increase in femoral neck BMD seen with alendronate alone (4.2% *vs.* 2.5%), no additional benefits were observed on BMD at other sites (52).

The effects of chronic ibutamoren (5, 10, 25 or 50 mg p.o. daily for 2-9 weeks) on serum IGF-I and markers of bone turnover were investigated in three randomized, double-blind, placebo-controlled studies in 187 elderly (65 years or older) healthy or functionally impaired (musculoskeletal) male and female adults. Treatment of healthy subjects with a dose of 10 or 25 mg for 2 weeks resulted in significant increases in mean urinary NTx of 10% and 17%, respectively, compared to placebo. Administration of 25 mg for 4 weeks or 25 mg for 2 weeks followed by 50 mg for 2 weeks to healthy subjects significantly increased serum osteocalcin (8%) and IGF-I (55-94%). Treatment of functionally impaired subjects with daily ibutamoren (5, 10 or 25 mg/day for 2 weeks followed by 25 mg for 7 more weeks) significantly increased mean serum osteocalcin (29.4%), bone-specific alkaline phosphatase (10.4%) and mean urinary NTx excretion (22.6%) by 9 weeks; ibutamoren-related changes in osteocalcin significantly correlated with changes in serum IGF-I (53).

A study examining the effects of ibutamoren (25 mg p.o. once daily for 6 months) on functional recovery from hip fracture in previously mobile older patients (65 years and older), failed to find any clinically significant improvement. The multicenter, randomized, double-blind, placebo-controlled, parallel-group study involved 161 patients recruited between 3 and 14 days postoperatively or no more than 18 days postfracture; patients were followed for 6 months after discontinuation of treatment. Treatment increased serum IGF-I by 84% as compared to 17% on placebo. However, no significant improvements in functional performance measures or on overall Sickness Impact Profile for Nursing Homes (SIP-NH) scores were observed. A tendency toward greater improvements was detected in the ibutamoren group as compared to placebo in 3 of 4 lower extremity functional performance measures, in the physical domain of SIP and in the ability to live independently. However, these differences did not reach statistical significance (54).

A randomized, double-blind, placebo-controlled, parallel-group phase II trial is recruiting patients to examine the efficacy, safety and tolerability of 24-week ibutamoren therapy in treating sarcopenia in hip fracture patients. The study will determine if ibutamoren can improve physical functional recovery in patients with recent hip fracture (55). Another randomized, double-blind, placebo-controlled, parallel-group phase II trial has been initiated and continues to recruit patients to examine the efficacy and safety of ibutamoren (25 mg) as a treatment for the symptoms of primary fibromyalgia (56). In addition, the effects of ibutamoren on memory and cognition in patients with Alzheimer's disease are also being investigated in a randomized, double-blind, placebo-controlled phase II trial (57).

Source

Merck & Co., Inc. (US).

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