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SOMATROGON: A LONG-ACTING GROWTH HORMONE ANALOG FOR PEDIATRIC GROWTH HORMONE DEFICIENCY – A COMPREHENSIVE REVIEW

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Abstract:

Growth hormone deficiency (GHD) is a clinically significant endocrine disorder characterized by impaired linear growth, delayed skeletal maturation, and metabolic abnormalities in pediatric populations. Recombinant human growth hormone (rhGH) therapy has been the cornerstone of management for several decades; however, the requirement for daily injections often leads to poor adherence and suboptimal clinical outcomes. Somatrogon is a novel long-acting recombinant growth hormone analog designed to reduce dosing frequency to once weekly while maintaining therapeutic efficacy. This review provides a detailed analysis of somatrogon, including its pharmacological profile, mechanism of action, pharmacokinetics, clinical efficacy, safety, and therapeutic advantages. Evidence suggests that somatrogon demonstrates non-inferiority to daily somatropin in improving height velocity, with comparable safety outcomes and improved patient compliance. The structural modification involving the addition of a C-terminal peptide prolongs its half-life and sustains insulin-like growth factor-1 (IGF-1) activity. Although currently approved for pediatric GHD, ongoing studies are evaluating its use in adult populations. Somatrogon represents a significant advancement in endocrine therapy, offering improved convenience and adherence without compromising efficacy.

Keywords: *Somatrogon, Growth hormone deficiency, Long-acting GH, IGF-1, Pediatric endocrinology*

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1. INTRODUCTION:

Growth hormone deficiency (GHD) is a disorder resulting from inadequate secretion of endogenous growth hormone, leading to impaired growth and developmental abnormalities in children. The condition is diagnosed based on clinical features such as reduced height velocity, delayed bone age, and biochemical evidence of low GH and insulin-like growth factor-1 (IGF-1) levels . In severe congenital cases, symptoms may include hypoglycemia, prolonged jaundice, and developmental delay, whereas milder forms present primarily with short stature and delayed puberty. The prevalence of pediatric GHD has been estimated to range between 1 in 3,500 and 1 in 4,000 children, highlighting its clinical significance .
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The somatotropic axis, comprising growth hormone and IGF-1, plays a central role in regulating growth and metabolism. GH stimulates hepatic production of IGF-1, which mediates most of the anabolic and growth-promoting effects. Disruption of this axis results in significant impairment in physical development. Recombinant human growth hormone (rhGH) therapy has been widely used for over six decades and has proven effective in restoring normal growth patterns. However, daily subcutaneous administration is associated with challenges including injection-related discomfort, psychological burden, and poor long-term adherence, particularly in pediatric populations.

Somatrogon has been developed as a long-acting GH analog to address these limitations. By extending the half-life of the hormone, it allows once-weekly administration, thereby reducing treatment burden and improving adherence . This advancement represents a significant step forward in optimizing the management of GHD.
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2. Drug Profile and Indications

Somatrogon is a recombinant human growth hormone analog designed for prolonged systemic activity. It is indicated for the treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone . The drug is formulated as a pre-filled pen for subcutaneous administration and is available in multiple strengths to facilitate individualized dosing based on patient characteristics such as body weight and treatment response .
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The U.S. Food and Drug Administration (FDA) approved somatrogon (Ngenla) in 2023 following clinical trials demonstrating its efficacy and safety. The approval was based on evidence showing that somatrogon is non-inferior to daily somatropin therapy in promoting growth in children with GHD . Its once-weekly dosing schedule offers a practical advantage over conventional therapies, making it particularly suitable for long-term pediatric use.
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3. Mechanism of Action

Somatrogon exerts its therapeutic effects by mimicking the action of endogenous growth hormone. Upon subcutaneous administration, it binds to growth hormone receptors located on target tissues, particularly in the liver, leading to activation of intracellular signaling pathways and stimulation of IGF-1 production . IGF-1 is the primary mediator of growth, promoting bone elongation, protein synthesis, and cellular proliferation.
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A distinctive feature of somatrogon is its molecular modification involving the addition of a C-terminal peptide (CTP) derived from human chorionic gonadotropin. This modification significantly prolongs the drug's half-life by reducing its rate of degradation and clearance . As a result, somatrogon provides sustained stimulation of IGF-1 production over an extended period, allowing for less frequent dosing while maintaining consistent therapeutic effects.
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4. Pharmacokinetics

The pharmacokinetic profile of somatrogon is optimized to support once-weekly dosing. Following subcutaneous administration, the drug is slowly absorbed into the systemic circulation, with a time to peak plasma concentration (Tmax) of approximately 24 hours and a bioavailability of around 80% . This gradual absorption contributes to a stable and prolonged pharmacodynamic effect, minimizing fluctuations in hormone levels.

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Distribution of somatrogon is largely confined to the extracellular fluid compartment due to its large molecular size, which limits its ability to cross cellular membranes . The drug primarily targets growth hormone receptors in hepatic tissue, where it exerts its biological effects.
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Unlike small-molecule drugs, somatrogon is not metabolized by hepatic cytochrome P450 enzymes. Instead, it undergoes proteolytic degradation into smaller peptides and amino acids, which are subsequently recycled or excreted . The elimination half-life of approximately 110 hours enables sustained systemic exposure and supports weekly dosing .

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5. Clinical Efficacy
Clinical studies evaluating somatrogon have demonstrated its effectiveness in promoting growth in children with GHD. Randomized controlled trials have shown that somatrogon is non-inferior to daily somatropin in increasing annual height velocity. Sustained IGF-1 levels achieved with weekly dosing contribute to consistent growth outcomes comparable to those observed with daily therapy.
An important advantage of somatrogon is improved treatment adherence. The reduction in injection frequency significantly decreases the physical and psychological burden associated with daily injections, leading to better compliance among pediatric patients and their caregivers. This improved adherence is expected to translate into better long-term clinical outcomes.

6. Safety and Adverse Effects
Somatrogon is generally well tolerated, with a safety profile similar to that of conventional growth hormone therapies. Common adverse effects include injection site reactions such as redness, swelling, and pain, as well as systemic symptoms such as headache, fatigue, and joint pain . These effects are typically mild and transient.
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Serious adverse effects are rare but may include intracranial hypertension, characterized by headache, visual disturbances, and nausea. Other potential complications include hyperglycemia and hypothyroidism, necessitating regular monitoring during treatment . The development of anti-drug antibodies has been reported but does not appear to significantly impact efficacy in most cases.
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7. Drug Interactions, Warnings, and Precautions
Somatrogon may influence the metabolism of drugs processed via cytochrome P450 enzymes, including corticosteroids and anticonvulsants . Additionally, it may affect insulin sensitivity, requiring adjustments in antidiabetic medications.
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Important precautions include avoiding use in patients with active malignancy, as growth hormone may promote tumor growth. Regular monitoring of thyroid function and blood glucose levels is recommended. IGF-1 levels should be periodically assessed to ensure appropriate dosing and avoid overtreatment .
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8. Toxicity and Overdose
Overdose of somatrogon may result in symptoms associated with excessive growth hormone activity, including abnormal growth of extremities, fluid retention, joint pain, and metabolic disturbances such as hyperglycemia . Long-term overdose may lead to complications such as cardiomegaly and insulin resistance.

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Management of overdose is primarily supportive and involves discontinuation of therapy, monitoring of clinical and biochemical parameters, and symptomatic treatment as required.

9. DISCUSSION:
Somatrogon represents a significant advancement in the treatment of pediatric GHD by addressing one of the major limitations of traditional therapy—poor adherence due to daily injections. Its extended half-life and sustained pharmacodynamic profile allow for once-weekly administration without compromising efficacy. Clinical evidence supports its non-inferiority to daily GH therapy, with comparable safety outcomes.

However, certain limitations remain, including the need for long-term safety data and evaluation in adult populations. Additionally, cost considerations and accessibility may influence its widespread adoption. Despite these challenges, somatrogon has the potential to improve treatment outcomes by enhancing adherence and patient satisfaction.

10. CONCLUSION
Somatrogon is a promising long-acting growth hormone analog that offers a convenient and effective alternative to daily GH therapy for pediatric GHD. Its pharmacological properties enable sustained therapeutic effects with reduced dosing frequency, improving adherence and overall treatment experience. Continued research is required to further establish its long-term safety and expand its clinical applications.

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