Drug Coverage Policy

Effective Date……07/01/2025
Coverage Policy Number……IP0577
Policy Title……Ngenla

Growth Disorders – Ngenla

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview
Ngenla, a human growth hormone (hGH) product, is indicated for the treatment of **growth failure due to inadequate secretion of growth hormone (GH)** in pediatric patients ≥ 3 years of age.[1]

Disease Overview

Ngenla is a hGH analog, which is made up of the amino acid sequence of hGH with an added three copies of the C-terminal peptide of human chorionic gonadotropin.[1] The addition of the C-terminal peptides leads to a longer half-life. Ngenla binds to the GH receptor, which initiates changes in growth and metabolism. In children with GH deficiency (GHD), somatropin is effective for increasing final adult height.[2] Somatropin therapy is recommended to normalize adult height and prevent extreme shortness in children and adolescents with GHD. In addition to congenital causes, hypopituitarism may also be caused by radiation therapy; somatropin may be used to improve final height of children who have undergone radiation.[3,4]

Guidelines
Current guidelines do not specifically address Ngenla. Neither the Pediatric Endocrine Society guidelines for children and adolescents with GHD[2] (2016) nor the GH Research Society guidelines on children with short stature[11] (2019) recommend a specific GH product for GHD. Guidelines recommend the use of GH to normalize adult height and prevent extreme shortness in pediatric patients with GHD.

Coverage Policy

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, and/or other information.

Policy Statement
Prior Authorization is required for prescription benefit coverage of Ngenla. All reviews will be directed to a clinician (i.e., pharmacist) for verification of criteria. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ngenla as well as monitoring required for adverse events and long-term efficacy, initial approval requires the patient to be evaluated by a physician who specializes in the condition being treated. hGH is FDA-approved for treatment of a limited number of conditions. The FDA has not approved the use of hGH as therapy for anti-aging, longevity, or cosmetic or performance enhancement. Federal law prohibits the dispensing of hGH for non-approved purposes. A pharmacy's failure to comply with that law could result in significant criminal penalties to the pharmacy and its employees. Accordingly, a pharmacy may decline to dispense prescriptions for hGH when written by a physician or other authorized prescribers who they believe may be involved in or affiliated with the fields of anti-aging, longevity, rejuvenation, cosmetic, performance enhancement, or sports medicine.

Ngenla is considered medically necessary when the following criteria is met:

1. **Growth Hormone Deficiency in a Pediatric Patient.** Individual meets **ALL** of the following criteria:
    A. 3 years of age to 17 years of age
    B. **ONE** of the following:
        i. Documentation of **BOTH** of the following:
            a. Diagnostic evaluation including **BOTH** of the following:
                I. Other pituitary hormone deficiencies (for example, thyroid, cortisol or sex steroids) have been ruled out and/or corrected prior to time of testing
                II. **TWO** growth hormone stimulation tests performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon **AND** both tests show a growth hormone response of less than 10 ng/mL

b. Auxologic evaluation (stature and growth velocity data) including **ONE** of the following:
    a. Height is more than two [2] standards of deviation (SD) below average for the population mean height for age and sex, and **ONE** of the following:
        1) One-year height velocity more than one standard of deviation (SD) below the mean for chronological age
        2) 2 years of age or older, and there is a decrease in height of more than 0.5 standards of deviation (SD) over one year
    b. One-year height velocity is more than two standards of deviation (SD) below the mean for age and sex
    c. Height velocity is more than 1.5 standards of deviation (SD) below the mean sustained over two years

ii. Cranial or Whole Body irradiation

iii. **BOTH** of the following:
    a. **ONE** of the following:
        I. Defined central nervous system pathology (for example, empty sella syndrome, interruption of pituitary stalk, hypoplasia of the pituitary gland, craniofacial developmental defects, pituitary or hypothalamic tumors)
        II. undergone tumor resection
    b. **ONE** of the following:
        I. **ONE** growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon **AND** the test shows a growth hormone response of less than 10 ng/mL
        II. Deficiency in at least **ONE** other pituitary hormone (for example, adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin [luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency], or prolactin)

iv. Congenital hypopituitarism

v. Multiple pituitary hormone deficiencies and **BOTH** of the following:
    a. **THREE** or more of the following pituitary hormone deficiencies: somatropin (growth hormone), adrenocorticotropic hormone, thyroid-stimulating hormone, gonadotropin (luteinizing hormone and/or follicle stimulating hormone deficiency are counted as one deficiency), and prolactin
    b. **ONE** growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon **AND** the test shows a growth hormone response of less than 10 ng/mL

Note: If the individual has had one growth hormone stimulation test and the peak growth hormone response was less than 10 ng/mL, this would satisfy criteria for an approval.

vi. Hypophysectomy (surgical removal of pituitary gland)

C. Medication is prescribed by, or in consultation with, an endocrinologist
D. Preferred product criteria is met for the products listed in the below table(s)

Employer Group Drug Lists:

Product	Criteria
Ngenla (somatrogon-ghla)	**Advantage/Value/Total Savings Drug List Plans:** Documented inadequate efficacy (following 6 months of therapy) or intolerance to **Skytrofa** [requires prior authorization]

Individual and Family Plans:

Product	Criteria
Ngenla (somatrogon-ghla)	Documented trial with inadequate efficacy (tried for 12 months and has a growth rate of less than 2 cm per year) with **Genotropin** [requires prior authorization]

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of somatrogon-ghla (Ngenla) is considered medically necessary for Growth Hormone Deficiency when the above medical necessity criteria are met AND beneficial response is demonstrated by **ONE** of the following:

1. Less than 12 years of age: Height has increased by at least 2 cm/year in the most recent year
2. 12 years of age to 17 years of age AND **BOTH** of the following:
    a. Height has increased by at least 2 cm/year in the most recent year
    b. Epiphyses are open

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Ngenla for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Athletic Ability Enhancement.** Somatropin and related agents are not FDA-approved for athletic performance enhancement or for body building in non-athletes. Federal law prohibits the distribution or dispensing of somatropin or related agents for non-FDA approved uses.

2. **Central Precocious Puberty.** Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (Lupron® [leuprolide acetate injection]) to suppress pituitary gonadal activity, to slow the advancement of bone age (prevent premature fusion of the epiphyseal growth plates), and to improve adult height. In some patients, GnRH agonist therapy may result in marked deceleration of bone growth and may result in adult height that is less than the midparental height. Somatropin has been used in girls when growth velocity decreases or if it appears that the targeted adult height will not be attained. There are no large well-controlled trials on the efficacy and safety of adding somatropin to GnRH agonist therapy in these children or the effect on final height.

3. **Congenital Adrenal Hyperplasia (CAH).** The Endocrine Society clinical practice guidelines on CAH due to steroid 21-hydroxylase deficiency recommend against the use of experimental treatment approaches outside of formally approved clinical trials. Children with predicted adult height standard deviation ≤ -2.25 may be considered for growth-promoting treatments in appropriately controlled trials.

4. **Constitutional Delay of Growth and Puberty.** These children have delayed skeletal maturation and pubertal development. Administering somatropin does not increase adult height (which is usually normal). Short-term androgen therapy accelerates growth and the rate of pubertal advancement in boys.

5. **Acute Critical Illness Due to Complications Following Surgery, Multiple Accidental Trauma, or with Acute Respiratory Failure.** In two placebo-controlled trials, in non-growth hormone deficient adults (n = 522) with these conditions, there was a significant increase in mortality (42% vs. 19%) in patients treated with somatropin compared to those on placebo.

6. **Aging (i.e., Antiaging); To Improve Functional Status in Elderly Patients; and Somatopause.** Somatropin is not FDA-approved for anti-aging therapy, to improve functional status in elderly patients, or to treat somatopause. Federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses. There are no long-term studies assessing somatropin efficacy and safety for anti-aging therapy. Short- Page 8 of 19 Coverage Policy Number: 4012 term therapy with somatropin may improve some measures of body composition, including increased muscle mass, reduced total body fat, improved skin elasticity, and reduced rate of bone demineralization, but does not have positive effects on strength, functional capacity, or metabolism. Somatropin is associated with considerable adverse effects in non-growth hormone deficient adults (e.g., carpal tunnel syndrome, soft tissue edema, arthralgias, glucose intolerance, increased serum lipids). Another concern is the possible increased risk of cancer with long-term use of somatropin and the potentiating effects of IGFs on cancer. Somatropin is not indicated for the age-related decrease in growth hormone/IGF-1 status.

7. **Chronic Fatigue Syndrome.** There is no evidence of GHD in chronic fatigue syndrome.

8. **Corticosteroid-Induced Short Stature.** This includes a variety of chronic glucocorticoid-dependent conditions, such as asthma, Crohn's disease, juvenile rheumatoid arthritis, as well

as after renal, heart, liver, or bone marrow transplantation. Short-term improvement in growth velocity in children with glucocorticoid-induced suppression has been reported with somatropin therapy. Long-term data are not available. Children being considered for treatment with somatropin should be enrolled in studies that allow careful monitoring and data analysis.

9. **Fibromyalgia.** In one placebo-controlled study, 120 non-GHD adult women with severe fibromyalgia and low levels of IGF-1 were randomized to somatropin 0.006 mg/kg/day for 12 months (dose was adjusted) or placebo for 6 months. Patients receiving placebo initially were switched to somatropin from Months 6 to 12 (open label). Standard therapy for fibromyalgia was continued. After 6 months, there were no differences between somatropin and placebo in the percentage of patients with fewer than 11 positive tender points, mean number of tender points, intensity of pain in every point evaluated, and other measures. After 12 months of somatropin therapy, 53% of patients had less than 11 positive tender points compared with 33% of patients who received placebo and then somatropin for 6 months ($P < 0.05$). At 18 months follow-up evaluation when somatropin was discontinued, impairment in pain perception worsened in both groups but to a lesser extent in the patients on somatropin for 12 months. Further controlled trials are needed with a longer duration, with different doses, and using the 2010 American College of Rheumatology criteria for fibromyalgia. Some patients with fibromyalgia may have adult GHD.

10. **Human Immunodeficiency Virus (HIV)-Infected Patients with Alterations in Body Fat Distribution** (e.g., increased abdominal girth, lipodystrophy and excess abdominal fat, buffalo hump). Somatropin is not indicated for the treatment of HIV-associated adipose redistribution syndrome (HARS). HARS is a subset of HIV lipodystrophy and is defined as maldistribution of body fat characterized by central fat accumulation (lipohypertrophy) with or without lipoatrophy. In HARS, fat may also accumulate in the upper body subcutaneous area such as the dorsocervical area (buffalo hump). These changes may be associated with metabolic disturbances (insulin resistance, glucose intolerance, dyslipidemia) and belly image distress. Safety and efficacy are not established.

11. **Infertility**. Clinical trials indicate that somatropin is not useful as an adjunct during in vitro fertilization, for induction of ovulation in polycystic ovary syndrome, or for assisted reproductive technology. The authors of a recent meta-analysis concluded there is no evidence of an increased chance of a live birth with use of somatropin.

12. **Obesity.** Somatropin is not indicated for the treatment of obesity. Low growth hormone levels are a consequence of central obesity and not a cause. Obesity is associated with decreased basal and pusatile release of growth hormone and decreased stimulated growth hormone release. Somatropin therapy does not have significant beneficial effects on obesity in persons without GHD and does not produce significant overall weight loss. Supraphysiologic doses of somatropin have been used to treat obesity. Effects of long-term therapy with somatropin are unknown.

13. **Osteoporosis.** Guidelines for treatment or prevention of osteoporosis do not include recommendations for use of somatropin. In one double-blind trial, 80 postmenopausal women with osteoporosis (56% of patients [n = 45/80] had a history of fractures) were randomized to somatropin 0.33 mg/day or 0.83 mg/day or to placebo for three years.50 The double-blind phase was 18 months and patients on somatropin continued drug for another 18 months and patients on placebo stopped at 18 months. Patients were compared with an age matched random population sample of women (n = 120). All patients received calcium 750 mg, vitamin D 400 units, and hormone replacement therapy. All women were followed for 10 years total. Bone mineral density increased in the patients receiving somatropin at years 4 and 5, and after 10 years, had decreased to similar levels as before treatment. At 10 years, 28% of

women (n = 22/80) had had fractures. In the control group, fractures increased from 8% of patients at baseline to 32% of patients after 10 years. At 10 years, 41% of patients (n = 33/80) had stopped hormone replacement therapy; 23% had started bisphosphonates due to fractures, and 3% had received Forteo® (teriparatide injection). Larger studies are needed to determine the effects of somatropin therapy on bone mineral density and fractures in non-growth hormone deficient persons.

14. **Other Off-label Uses [for example, celiac disease, chromosomal anomalies unless otherwise specified as covered (for example, but not limited to, deletion of chromosome 18q), Crohn's disease, cystic fibrosis, Down syndrome, hypophosphatemic rickets, juvenile rheumatoid arthritis, muscular dystrophy, primary or idiopathic IGF-1 deficiency, skeletal dysplasias, spinal cord defects].** There is insufficient evidence in the peer-reviewed published scientific literature to support the safety and efficacy of growth hormone therapy in these conditions. Additionally, federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses.

References

1. Ngenla® subcutaneous injection [prescribing information]. New York, NY: Pfizer; June 2023.
2. Grimberg A, DiVall SA, Polychronakos C, et al; Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. *Horm Res Paediatr*. 2016;86(6):361-397.
3. Melmed S. Idiopathic adult growth hormone deficiency. *J Clin Endocrinol Metab.* 2013;98:2187-2197.
4. Isfan F, Kanold J, Merlin E, et al. Growth hormone treatment impact on growth rate and final height of patients who received HSCT with TBI or/and cranial irradiation in childhood: a report from the French Leukaemia Long-Term Follow-Up Study (LEA). *Bone Marrow Transplant.* 2012;47:684-693.
5. Clemmons DR, Molitch M, Hoffman AR, et al. Growth hormone should be used only for approved indications. *J Clin Endocrinol Metab.* 2014;99:409-411.
6. Wang M, Zhang Y, Lan D, et al. The efficacy of GnRHa alone or in combination with rhGH for the treatment of Chinese children with central precocious puberty. *Sci Rep.* 2016. PMID: 27072597.
7. Fu J, Zhang J, Chen R, et al. Long-term outcomes of treatment for central precocious puberty or early and fast puberty in Chinese girls. *J Clin Endocrinol Metab.* 2020. PMID: 31702013.
8. Lin-Su K, Harbison MD, Lekarev O, et al. Final adult height in children with congenital adrenal hyperplasia treated with growth hormone. *J Clin Endocrinol Metab.* 2011;96:1710-1717.
9. Speiser PW, Arlt W, Auchus RJ, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018:103(11):4043-4088.
10. De Luca F, Argente J, Cavallo L, et al; International Workshop on Management of Puberty for Optimum Auxological Results. Management of puberty in constitutional delay of growth and puberty. *Pediatr Endocrinol Metab.* 2001;14 Suppl 2:953-957.
11. Collett-Solberg PF, Ambler G, Backelijaw PF, et al. Diagnosis, genetics, and therapy of short stature in children: A growth hormone research society international perspective. *Horm Res Paediatr.* 2019;92(1):1-14.

Revision Details

Type of Revision	Summary of Changes	Date
Selected Revision	**Removed** preferred product requirements from the Standard, Value and Legacy formularies.	03/15/2024
Selected Revision	**Updated** Individual and Family Plan preferred product requirements.	01/01/2025
Selected Revision	**Updated** the Employer Plans preferred product requirements. **Updated** the conditions not covered statement.	07/01/2025

The policy effective date is in force until updated or retired.