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FDA Approves Pfizer's NGENLA™, a Long-Acting Once-Weekly Treatment for Pediatric Growth Hormone Deficiency

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New, longer-acting treatment offers option to reduce the frequency of injections for children with growth hormone deficiency from daily to once-weekly

NEW YORK & MIAMI--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) and OPKO Health Inc. (NASDAQ: OPK) announced today that the U.S. Food and Drug Administration (FDA) has approved NGENLA (somatrogon-ghla), a once-weekly, human growth hormone analog indicated for treatment of pediatric patients aged three years and older who have growth failure due to inadequate secretion of endogenous growth hormone. NGENLA is expected to become available for U.S. prescribing in August 2023.

Growth hormone deficiency (GHD) is a rare disease characterized by the inadequate secretion of the growth hormone somatropin from the pituitary gland, affecting one in approximately 4,000 to 10,000 children.[1,2] Without treatment, children will have persistent growth attenuation, a very short height in adulthood, and puberty may be delayed.[1,2,3] Children living with GHD may also experience challenges in relation to their physical health and mental well-being.[1,2,3]

"For more than 30 years, Pfizer has been committed to supporting children and adults living with growth hormone deficiency, beginning with the delivery of a medicine that has long been a part of the standard of care," said Angela Hwang, Chief Commercial Officer, President, Global Biopharmaceuticals Business, Pfizer. "We are excited to bring this next-generation treatment to patients in the United States, continuing our commitment to helping children living with this rare growth disorder reach their full potential."

The FDA approval is supported by results from a multi-center, randomized, open-label, active-controlled Phase 3 study which evaluated the safety and efficacy of NGENLA when administered once-weekly compared to once-daily somatropin. The study met its primary endpoint of NGENLA non-inferiority compared to somatropin, as measured by annual height velocity at 12 months. NGENLA was generally well tolerated in the study and had a safety profile comparable to somatropin.

"The approval of NGENLA will be significant for children with growth hormone deficiency in the U.S. It holds potential to reduce the treatment burden that can come with daily growth hormone injections," said Joel Steelman, M.D., Pediatric Endocrinologist, Cook Children's Health Care System. "As a new, longer-acting option that has the ability to reduce treatment frequency from daily to weekly, NGENLA could become an important treatment option that can improve adherence for children being treated for growth hormone deficiency."

“Throughout our collaboration with Pfizer, we have worked tirelessly toward our shared goal of helping children living with growth hormone disease and their families,” said Phillip Frost, M.D., Chairman and Chief Executive Officer, OPKO Health. “We are proud of the clinical development program that supported the FDA approval of NGENLA and are excited about its potential for these patients and their families as it becomes available in the United States.”

NGENLA is approved for the treatment of pediatric GHD in more than 40 markets including Canada, Australia, Japan, and EU Member States.

The full Prescribing Information can be found here. If it is not currently available via this link, it will be visible as soon as possible as we work to finalize the document. Please check back for the full information shortly.

About NGENLA(somatrogon-ghla) Injection

NGENLA (somatrogon-ghla) is a human growth hormone that works by replacing the lack of growth hormone in the body. NGENLA is taken by injection just below the skin, administered via a device that allows for titration based on patient need. Compared to the growth hormone GENOTROPIN® (somatropin), its action in the body lasts longer, enabling weekly injections instead of daily.

In 2014, Pfizer and OPKO entered into a worldwide agreement for the development and commercialization of NGENLA for the treatment of GHD. Under the agreement, OPKO is responsible for conducting the clinical program and Pfizer is responsible for registering and commercializing NGENLA for GHD.

About the NGENLA Clinical Program
The safety and efficacy of NGENLA (somatrogon-ghla) was demonstrated in a multi-center, randomized, open-label, active-controlled Phase 3 study (NCT 02968004). The Phase 3 study enrolled and treated 224 pediatric patients, treatment-naïve children with growth hormone deficiency who were randomized 1:1 into two arms: NGENLA (somatrogon-ghla) once-weekly at a dose of 0.66 mg/kg/day vs somatropin, once-daily at a dose of 0.034 mg/kg/day. The study met its primary endpoint of NGENLA non-inferiority compared to somatropin, measured by annual height velocity at 12 months.

About Growth Hormone Deficiency
Growth hormone deficiency is a rare disease characterized by the inadequate secretion of growth hormone from the pituitary gland and affects one in approximately 4,000 to 10,000 children.[1,2] In children, this disease can be caused by genetic mutations or acquired after birth.[1,4] Because the patient's pituitary gland secretes inadequate levels of somatropin, the hormone that causes growth, a child’s height may be affected and puberty may be delayed.[1,2,5] Without treatment, affected children will have persistent growth attenuation and a very short height in adulthood.[1,2] Children may also experience challenges in relation to physical health and mental well-being.[1,2]

Important NGENLA (somatrogon-ghla) Safety Information

- Growth hormone should not be used in children after the growth plates have closed.
- Growth hormone should not be used in children with some types of eye problems caused by diabetes (diabetic retinopathy).
- Growth hormone should not be used in children who have cancer or other tumors.
- Growth hormone should not be used in children who are critically ill because of some types of heart or stomach surgery, trauma, or breathing (respiratory) problems.
- Growth hormone should not be used in children with Prader-Willi syndrome who are very overweight or have breathing problems including sleep apnea.

- NGENLA should not be used by children who have had an allergic reaction to somatrogon-ghla or any of the ingredients in NGENLA. Look for prompt medical attention in case of an allergic reaction.
- Some children have developed diabetes mellitus while taking growth hormone. Dosages of diabetes medicines may need to be adjusted during treatment with NGENLA. Children should be watched carefully if NGENLA is given along with glucocorticoid therapy and/or other drugs that are processed by the body in the same way.
- In childhood cancer survivors, treatment with growth hormone may raise the likelihood of a new tumor, particularly some benign (non-cancerous) brain tumors. This likelihood may be higher in children who were treated with radiation to the brain or head. Your child's health care provider will need to check your child for a return of cancer or a tumor.
- Children treated with growth hormone have had increased pressure in the brain. If your child has headaches, eye problems, nausea (feeling like you are going to be sick), or vomiting, contact your child's health care provider.
- NGENLA may decrease thyroid hormone levels. Decreased thyroid hormone levels may change how well NGENLA works. Your child's health care provider will do blood tests to check your child's hormone levels.
- Children treated with growth hormone should be checked regularly for low serum cortisol levels and/or the need to increase the dose of the glucocorticoids they are taking.
- In children experiencing fast growth, curvature of the spine may develop or worsen. This is also called scoliosis. Children with scoliosis should be checked regularly to make sure their scoliosis does not get worse during their growth hormone therapy.
- Use a different area on the body for each injection. This can help to avoid skin problems such as lumpiness or soreness.
- Growth hormone treatment may cause serious and constant stomach (abdominal) pain. This could be a sign of pancreatitis. Tell your child's health care provider if your child has any new stomach (abdominal) pain.
- In studies of NGENLA in children with GHD, side effects included injection site reactions such as pain, swelling, rash, itching, or bleeding. Other side effects were the common cold, headache, fever (high temperature), low red blood cells (anemia), cough, vomiting, decreased thyroid hormone levels, stomach pain, rash, or throat pain.
- A health care provider will help you with the first injection. He or she will also train you on how to inject NGENLA.
- Rx only

About GENOTROPIN(somatropin)
GENOTROPIN is a man-made, prescription treatment option. The indications GENOTROPIN is approved for vary by market. GENOTROPIN is approved for growth failure due to GHD and adult GHD, Prader-Willi Syndrome, Idiopathic Short Stature, Turner Syndrome, Small for Gestational Age (with no catch-up growth), and Chronic Renal Insufficiency. GENOTROPIN is taken by injection just below the skin and is available in a wide range of devices to fit a range of individual dosing needs. GENOTROPIN is just like the natural growth hormone that our bodies make and has an established safety profile.

Important GENOTROPIN (somatropin) Safety Information

- Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.
- Somatropin is contraindicated in patients with active proliferative or severe nonproliferative diabetic retinopathy.
- Somatropin is contraindicated in patients with active malignancy. Because growth hormone deficiency may be a sign of pituitary or other brain tumors, the presence of such tumors should be ruled out before

treatment is initiated. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

- Somatropin in pharmacologic doses should not be used to treat patients with acute critical illness due to complications from open heart surgery, abdominal surgery or multiple accidental traumas, or those patients with acute respiratory failure due to an increased mortality. The safety of continuing replacement somatropin treatment for approved uses in patients who develop these illnesses has not been established.
- Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have respiratory impairment.
- GENOTROPIN is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs.
- New-onset Type-2 diabetes mellitus has been reported. Monitor patients with glucose intolerance closely; dosage of antihyperglycemic drug may need to be adjusted. Monitor carefully if somatropin is administered in combination with glucocorticoid therapy and/or other drugs metabolized by the CP450 pathway.
- In childhood cancer survivors, an increased risk of a second neoplasm, in particular meningiomas, has been reported in patients treated with somatropin after their first neoplasm, particularly those who were treated with cranial radiation. Children with certain rare genetic causes of short stature have an increased risk of developing malignancies. Practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients and if treatment is initiated, should carefully monitor these patients for development of neoplasms. Patients should be monitored carefully for any malignant transformation of skin lesions.
- Intracranial hypertension (IH) has been reported in a small number of patients treated with somatropin. If papilledema is observed during somatropin treatment, treatment should be stopped and reassessed. Patients with Turner syndrome and Prader-Willi syndrome may be at increased risk for the development of IH.
- Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with growth hormone deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests, and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.
- Patients treated with somatropin who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking central hypoadrenalism and should be monitored for reduced serum cortisol levels. In addition, patients treated with glucocorticoid replacement for pre-existing hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment and should be monitored for reduced cortisol levels and/or need for glucocorticoid dose increases.
- Progression of scoliosis can occur in patients who experience rapid growth. Patients with scoliosis should be monitored for manifestation or progression during somatropin therapy.
- Slipped capital femoral epiphyses may occur more frequently in patients with endocrine disorders (including GHD and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.
- Somatropin should be used during pregnancy only if clearly needed and with caution in nursing mothers because it is not known whether somatropin is excreted in human milk.
- Subcutaneous injection of somatropin at the same site repeatedly may result in tissue atrophy. This can be avoided by rotating the injection site.

- Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops persistent severe abdominal pain.
- In clinical trials with GENOTROPIN in pediatric GHD patients, the following events were reported infrequently: injection site reactions, including pain or burning associated with the injection, fibrosis, nodules, rash, inflammation, pigmentation, or bleeding; lipoatrophy; headache; hematuria; hypothyroidism; and mild hyperglycemia.
- In clinical studies of 273 pediatric patients born SGA treated with GENOTROPIN, the following clinically significant events were reported: mild transient hyperglycemia; 1 patient with benign intracranial hypertension; 2 patients with central precocious puberty; 2 patients with jaw prominence; and several patients with aggravation of preexisting scoliosis, injection site reactions, and self-limited progression of pigmented nevi. Anti-hGH antibodies were not detected in any of the patients treated with GENOTROPIN.
- Deaths have been reported with the use of a growth hormone in pediatric PWS patients with severe obesity, history of upper airway obstruction or sleep apnea, and/or unidentified respiratory infection. Therefore, all patients with PWS should be evaluated and monitored for signs of upper airway obstruction, sleep apnea, and respiratory infections, and have effective weight control.
- In clinical trials with GENOTROPIN in pediatric patients with PWS, the following drug-related events were reported: edema, aggressiveness, arthralgia, benign intracranial hypertension, hair loss, headache, and myalgia.
- Somatropin may increase the occurrence of otitis media in Turner syndrome patients. In 2 clinical studies with GENOTROPIN in pediatric patients with Turner syndrome, the most frequently reported adverse events were respiratory illnesses (influenza, tonsillitis, otitis, sinusitis), joint pain, and urinary tract infection. The only treatment-related adverse event that occurred in more than 1 patient was joint pain.
- In 2 clinical studies with GENOTROPIN in pediatric patients with ISS, the most commonly encountered adverse events included upper respiratory tract infections, influenza, tonsillitis, nasopharyngitis, gastroenteritis, headaches, increased appetite, pyrexia, fracture, altered mood, and arthralgia.
- In clinical trials with GENOTROPIN in adults with GHD, the majority of side effects were symptoms of fluid retention, including peripheral swelling/edema, arthralgia, pain and stiffness of the extremities, myalgia, paresthesia, and hypoesthesia. Generally, these were transient and dose-dependent.
- In women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal.
- Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to develop adverse reactions.
- The cartridges of GENOTROPIN contain m-Cresol and should not be used by patients with a known sensitivity to this preservative.
- Subcutaneous injection of somatropin at the same site repeatedly may result in tissue atrophy. This can be avoided by rotating the injection site.
- Health care providers should supervise the first injection and provide appropriate training and instruction for the proper use of all devices for GENOTROPIN.
- Rx only

For the full Prescribing Information for GENOTROPIN, please visit http://labeling.pfizer.com/ShowLabeling.aspx?id=577.

Pfizer Inc.: Breakthroughs that Change Patients' Lives

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly

improve their lives. We strive to set the standard for quality, safety, and value in the discovery, development, and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments, and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments, and local communities to support and expand access to reliable, affordable health care around the world. For more than 170 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

About OPKO Health
OPKO is a multinational biopharmaceutical and diagnostics company that seeks to establish industry-leading positions in large, rapidly growing markets by leveraging its discovery, development, and commercialization expertise and novel and proprietary technologies. For more information, visit www.opko.com.

DISCLOSURE NOTICE: The information contained in this release is as of June 28, 2023. Pfizer and OPKO assume no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about NGENLA (somatrogon-ghla) injection and the U.S. FDA approval to treat pediatric patients aged three years and older with growth failure due to inadequate secretion of endogenous growth hormone, including its potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the commercial success of NGENLA; the uncertainties inherent in research and development, including the ability to meet anticipated regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when drug applications may be filed in any additional jurisdictions for NGENLA injection for the treatment of pediatric patients with growth hormone deficiency or in any jurisdictions for any other potential indications for NGENLA injection; whether and when regulatory authorities in any jurisdictions may approve any applications that may be pending or filed for NGENLA, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether NGENLA injection will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of NGENLA injection; uncertainties regarding the impact of COVID-19 on Pfizer's and OPKO's respective business, operations and financial results; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's and OPKO's respective Annual Report on Form 10-K for the fiscal year ended December 31, 2022 and in their respective subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in their subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov , and www.pfizer.com in the case of Pfizer, and www.opko.com in the case of OPKO .

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