CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761184
PDUFA Goal Date	May 22, 2023
Nexus TTT #	2022-2874, 2022-2872
Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	May 19, 2023
Subject	Evaluation of Need for a REMS
Established Name	Somatrogon-ghla
Trade Name	Ngenla
Name of Applicant	Pfizer Ireland Pharmaceuticals
Therapeutic Class	Human growth hormone analog
Formulation(s)	24 mg/1.2 mL single-patient-use prefilled pen which delivers doses in 0.2 mg increments; 60 mg/1.2 mL single-patient-use prefilled pen which delivers doses in 0.5 mg increments
Dosing Regimen	Starting dose of 0.66 mg/kg body weight per week subcutaneously; then individualize for patient based on growth response; administer at the same time on the same day each week

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Ngenla (somatrogon-ghla) is necessary to ensure the benefits outweigh its risks. Pfizer Ireland Pharmaceuticals submitted a Biologic Licensing Application (BLA) 761184 for somatrogon-ghla with the proposed indication for the treatment of pediatric patients aged 3 years and older who have growth failure due to inadequate secretion of endogenous growth hormone.[1] The risks associated with somatrogon-ghla include the following risks: increased mortality in acute illness and Prader-Willi Syndrome, serious hypersensitivity reactions, increased risk of neoplasm, glucose intolerance and diabetes mellitus, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis, progression of preexisting scoliosis, pancreatitis, and lipoatrophy. The applicant did not submit a REMS with this application but included a proposed risk management plan and an active surveillance study to monitor long-term safety in European patients.

DRM and the Division of General Endocrinology (DGE) have determined that a REMS is not needed to ensure the benefits of somatrogon-ghla outweigh its risks. The serious risks associated with somatrogon are class-wide and will be managed via warnings and precautions in the label as with the other products in the class. Labeling for somatrogon will also include contraindications for patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment, acute critical illness, closed epiphyses, hypersensitivity to somatrogon or excipients, active malignancy, and active proliferative or non-proliferative diabetic retinopathy. These contraindications are also seen in other growth hormone products.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new biologic product[a] Ngenla (somatrogon-ghla) is necessary to ensure the benefits outweigh its risks. Pfizer Ireland Pharmaceuticals submitted a Biologic Licensing Application (BLA) 761184 for somatrogon-ghla (somatrogon) with the proposed indication for the treatment of pediatric patients aged 3 years and older who have growth failure due to inadequate secretion of endogenous growth hormone. This application is under review in the Division of General Endocrinology (DGE) as a class 2 resubmission. The applicant did not submit a REMS with this application but included a proposed risk management plan and an active surveillance study to monitor long-term safety in European patients.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2. Background

2.1. Product Information

Somatrogon is a new biologic product, submitted under section 351(a) of the Public Health Act. Somatrogon is a drug-device combination product, with human growth hormone analogue in a disposable prefilled pen injector. Somatrogon's proposed indication is for the treatment of pediatric patients aged 3 years and older who have growth failure due to inadequate secretion of endogenous growth hormone (GH).[1]

Somatrogon is proposed as a long-acting recombinant human growth hormone (hGH) modified with a fusion of its carboxy-terminal peptide (CTP). The active portion of somatrogon is the same primary amino acid sequence as human endogenous human growth hormone. As such, it is expected somatrogon will have the same binding to and activation of human growth receptors as endogenous hGH. This, in turn, causes transcription of genes for multiple proteins, including insulin-like growth factor (IGF-1). Both growth hormone and IGF-1 stimulate growth by stimulating epiphyseal growth plates and formation of new bone until growth plate closure.[2]

Somatrogon is proposed as a starting dose of 0.66 mg/kg body weight per week subcutaneously via a single-patient use, disposable, pre-filled pen, and the dose may then be individualized for patient based on growth response. The Pediatric Endocrine Society recommends growth hormone therapy should not continue beyond growth velocity below 2.0 to 2.5 cm/yr, usually in late puberty.[3] Somatrogon should be administered at the same time on the same day each week.[b] Somatrogon is proposed to be available in 2 strengths; a 24 mg/1.2 mL single-patient-use prefilled pen that delivers doses in 0.2 mg increments, and 60 mg/1.2 mL single-patient-use prefilled pen that delivers doses in 0.5 mg increments.[1]

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761184 relevant to this review:

- 09/29/2010: Orphan Drug Designation granted for somatrogon[4]
- 10/22/2020: BLA 761184 submission (b) (4) (b) (4) received
- 05/04/2021: In the Mid-cycle Communication sent from the Agency to the applicant, the review team stated that, "at this time no new adverse reactions associated with the use of this drug have been identified and a risk evaluation and mitigation strategy (REMS) is not being considered"[5]
- 09/15/2021: The applicant submitted further safety, efficacy, and immunogenicity data[6]

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 09/23/2021: The Agency informed the applicant the information submitted on September 15, 2021, constituted a Major Amendment[7]
- 01/21/2022: The Agency sent a Complete Response letter citing deficiencies including "immunogenicity effects that may decrease the efficacy and potentially affect the long-term safety of somatrogon," the development of anti-carboxy terminal peptide (anti-CTP) antibodies that may interfere with human chorionic gonadotropin based diagnostic assays, incomplete facilities inspections due to travel restrictions in Agency travel[8]
- 11/22/2022: BLA 761184 complete response submitted (b) (4) received

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Growth hormone deficiency (HGD) is caused by insufficient pituitary gland production of growth hormone, which results in less circulating growth hormone and insulin-like growth factor in the body. The lower amount of circulating GH means that fewer receptors are stimulated to prompt epiphyseal growth plate stimulation and formation of new bone. This causes short stature, delayed puberty and bone age, and results in decreased adult height. Patients may also exhibit hypoglycemia, jaundice, craniofacial abnormalities, and microphallus.[c] The prevalence of pediatric GHD is estimated to be 1:4000 to 1:10,000 children.[9],[d] Growth hormone deficiency may be secondary to acquired causes (trauma, tumors), congenital causes (genetic disorders, pituitary hypoplasia), or idiopathic.[10]

3.2. Description of Current Treatment Options

The Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society Guidelines on Growth Disorders and their Treatment recommends treatment of GHD in childhood with growth hormone replacement therapy to normalize patients' height during childhood and that they may achieve normal adult height in the future.[3] The FDA first approved growth hormone replacement therapies for pediatric patients with an endogenous growth hormone deficiency in 1985, and multiple somatropin formulations have been approved since then, including Humatrope in 1986, Omnitrope and

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Genotropin in 1987, Nutropin in 1994, Zomacton in 1995, and Norditropin in 2000. Earlier formulations required daily subcutaneous injections, which cause increased injection-related pain in pediatric patients and may contribute to noncompliance. Two long-acting formulations, Skytrofa (lonpegsomatropin-tcgd), approved August 25, 2021, and Sogroya (somapacitan-beco), approved for pediatric use in pediatric patients ages 2.5 years and older April 28, 2023, allow for once weekly subcutaneous dosing.[11,12]

With decades of use of approved products, known common side effects of growth hormone included in warnings and precautions in labeling are increased mortality in acute illness and Prader-Willi Syndrome, serious hypersensitivity reactions, intracranial hypertension, slipped capital femoral epiphysis, progression of scoliosis, diabetes and impaired glucose tolerance, pancreatitis, arthralgia, fluid retention, risk of neoplasm, and lipoatrophy. Previously undiagnosed hypothyroidism and adrenal insufficiency may be noted once growth hormone therapy begins.[11,12]

4. Benefit Assessment

In the ongoing clinical review, the clinical reviewer states that "somatrogon is effective in improving annual height velocity (AHV) in pediatric GHD." [12,e]

The applicant submitted one pivotal phase 3 study (CP-4-006, NCT 02968004) and one phase 2 study (CP-4-004, NCT 01592500) in support of this application. The primary data for the efficacy and safety of somatrogon is provided by the randomized, 12-month portion of the phase 3 trial with confirmatory data provided by the 12-month main period of the phase 2 study. Long-term efficacy and safety data is provided from both the phase 3 (up to 3 years) and phase 2 (up to 7 years) studies' uncontrolled extension periods. Study CP-4-006 was an open-label, multicenter study of 224 subjects who were treatment naïve, pre-pubertal, with short stature due to GHD that were randomized 1:1 to either somatrogon or Genotropin, with a primary efficacy endpoint of annual height velocity (AHV), which is the difference in height from baseline at Week 52 of somatrogon therapy as compared to Genotropin. The open-label extension (OLE) period enrolled 212 subjects (104 originally randomized to somatrogon and 108 originally randomized to Genotropin), 102 of which completed 2 years of somatrogon treatment, and 13 subjects completed 3 years of somatrogon therapy. CP-4-004 was a randomized, multicenter, open-label, dose-finding study with a primary endpoint of AHV measured at Week 52 of treatment. Fifty-six subjects were randomized 1:1:1:1 to somatrogon 0.25 mg/kg/wk, somatrogon 0.48 mg/kg/wk/, somatrogon 0.66 mg/kg/wk, and Genotropin 0.034 mg/kg/day. This study also included an OLE, which will provide up to 7 years of safety and efficacy data.[2,13]

In Study CP-4-006, somatrogon was non-inferior to Genotropin. Subjects using somatrogon had a mean AHV at Week 52 of 10.07 cm/yr., and those using Genotropin had a mean AHV of 9.73 cm/yr. The difference between the 2 means was 0.34 cm/yr. (95% Confidence Interval [CI] -0.23,0.91).[2] As the lower

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

limit of the 95% CI was greater than the prespecified non-inferiority margin of ≥ -1.8cm/yr., somatrogon was non-inferior to Genotropin.[12] Data from the second year demonstrated the continued effect on AHV, with 9.1 cm/yr. (range 5.55, 14.32 cm/yr.) mean AHV in the 2-year somatrogon use subjects, and 8.98 cm/yr. (Range 5.51, 13.98 cm/yr.) in subjects who used Genotropin year 1 and somatrogon year 2.

Study CP-4-004 provided confirmatory data, as seen in Table 1, with all three doses of somatrogon providing dose-dependent increases in AHV, which were numerically smaller than subjects treated with Genotropin.

Table 1: Week 52 AHV in Each Treatment Group

	Somatrogon 0.25 mg/kg/wk	**Somatrogon 0.48 mg/kg/wk**	**Somatrogon 0.66 mg/kg/wk**	**Genotropin 0.034 mg/kg/wk**
Week 52 Mean AHV (cm/yr)	10.4	11.0	11.4	12.5
95% CI	8.9, 12.0	9.7, 12.2	9.2, 13.7	11.0, 13.9

Adapted from the Division of General Endocrinology Integrated Review of Somatrogon, January 21, 2022

4.1. Immunogenicity

The Agency had concerns with the high immunogenicity demonstrated in the initial submission and additional 12-month safety and efficacy data provided in the September 15, 2021 safety update.[6] The January 21, 2022, Complete Response Letter from the Agency noted the concerns of the high rate and persistence of antidrug antibodies (ADAs) to somatrogon and the potential for loss of efficacy due to this. In the first 12 months of Study CP-4-006, 77% of subjects taking somatrogon developed ADAs as compared to 16% of subjects in the Genotropin group.[13] The Agency also stated a concern regarding the ADAs potentially being cross-reactive to other GH products, resulting in loss of response to multiple therapies. Also listed in the Complete Response Letter were product quality deficiencies (b) (4) (b) (4)

To resolve the immunogenicity issues, a Type A teleconference was held with the applicant on March 22, 2022, and the Agency requested the following: additional immunogenicity assessment and analyses of the effect of antibody status on efficacy and safety on subjects in Studies CP-4-004 and -006 up to March 31, 2022, an assessment of subjects who discontinued Study CO-4-006 and had positive ADA at discontinuation, information on subject (b) (6) who experienced significant growth reduction upon conversion to positive neutralizing antibodies (NAb), and immunogenicity assessments of antibody status of subjects in Study CP-4-009 (NCT 03874013), a study of Japanese patients with pediatric GHD (not included in original assessment).[8] Study CP-4-009, a Phase 3, randomized, active-controlled, 12-month study of 44 Japanese pre-pubertal children with GHD randomized 1:1 to receive somatrogon and Genotropin. The initial 12-month study was followed by another 12-month OLE.

Data in the Complete Response from Pfizer also included the requested immunogenicity analyses, information on Study CP-4-009 and data for Study CP-4-006 OLE years 2 and 3, and Study CP-4-004 OLE years 6 and 7.[12] In Study CP-4-006, ADAs continued to be elevated with 84% of subjects who used somatrogon the entire study having ADAs by the end of OLE Year 1, and subjects who started the study

on Genotropin but switched to somatrogon also showed increased ADAs with somatrogon use, but were overall lower than subjects who used somatrogon throughout the study and OLE (55% at end of OLE Year 1). Subjects who tested positive for ADAs most often showed specificity to hGH, with few showing specificity to CTP, and once subjects had ADAs, they typically remained ADA positive. Eight subjects in CP-4-006 had NAbs throughout the 3 years of study, however 6 out of the 8 at one assessment only subsequently tested negative. Data from subjects who were ADA positive, then discontinued somatrogon suggests that ADAs resolve over time. In Study CP-4-004, ADA positivity at OLE Years 3 and 4 was 38.7% and 42% respectively, which is similar to the OLE Year 1 and 2 (38% and 37%, respectively). No NAbs were reported in CP-4-004. Subjects' immunogenicity in Study CP-4-009 was consistent with Study CP-4-006, with 81% of subjects taking somatrogon and 18% of subjects taking Genotropin developing ADAs by month 12. Two subjects developed transient NAbs. Data from subjects who discontinued somatrogon use suggests that ADAs resolve or decrease over time, and with limited data on subjects who discontinued somatrogon and started another growth hormone therapy, the impact of ADAs on other formulations could not be assessed accurately. Testing ADA positive did not have a negative effect on AHV. One subject, (b) (6) experienced NAbs during the previous review cycle, also experienced a significant AHV decrease. The subject underwent genetic testing and was shown to have deletion of the GH1 gene. As these patients are never exposed to hGH during fetal development, they develop immunological intolerance to GH and develop anti-GH antibodies following GH exposure. The decline of this subject's AHV can be attributed to this genetic cause, as opposed to somatrogon's immunogenicity. The continuation of growth data during OLE years suggests ADAs and NAbs do not have a meaningful impact on AHV.[12,14]

5. Risk Assessment & Safe-Use Conditions

The primary source of safety data for somatrogon is from the main phase, or first year, of Study CP-4-006, which will be used for labeling, and it was deemed adequate to discern any ADA-related safety concerns by the Agency.[13] The safety data from OLE of CP-4-004 and CP-4-006 are supportive and will not be used in the label.[12]

During the original submission of BLA 761184, staff from the Center for Devices and Radiological Health (CDRH) reviewed the proposed disposable pre-filled pen injector, and found no deficiencies, and determined any risks and instructions for use could be managed via labeling.[12]

ADA status did not cause an imbalance of adverse event frequency in the safety database.[13]

There were no deaths during the main phases or initial OLE periods of CP-4-006 or 004.

There were 3 serious adverse events (SAE) in the main phase of CP-4-006 in subjects using somatrogon. These include chronic tonsilitis, gastroenteritis, and pneumonia and 2 SAEs in those using Genotropin, which were tonsilitis and ureterolithiasis. The clinical reviewer noted that these appear common for the age group, as opposed to causation by somatrogon.

The most commonly reported (>5% of patients using somatrogon) adverse events were injection site reactions, nasopharyngitis, headache, pyrexia, anemia, cough, vomiting, abdominal pain, rash, and oropharyngeal pain.[f]

Adverse events that somatrogon has in common with currently approved recombinant human growth hormone derivatives due to class effects will be communicated in the warnings and precautions section of the label. These adverse events include increased mortality in patients with acute critical illness and Prader Willi syndrome with either severe obesity or severe pulmonary impairment, severe hypersensitivity, increased risk of neoplasm, glucose intolerance/diabetes mellitus, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis, progression of preexisting scoliosis, pancreatitis, and lipoatrophy. Select adverse events that were observed in the clinical trials are described below.

5.1. Severe Hypersensitivity

In CP-4-006, one subject discontinued the study due to an injection site reaction of erythema and indurations one day after an injection and resolved on Day 63. During the first year OLE, 5 subjects discontinued prematurely due to injection site reactions. During Study CP-4-006 OLE years 1-3, the frequency of hypersensitivity reactions was <10%, and similar between subjects who were ADA positive and ADA negative. All AEs of hypersensitivity, except for 1 case of severe urticaria, were nonserious, mild/moderate, most were self-limiting, and none required discontinuation of somatrogon.[12] As GH products can cause severe hypersensitivity, somatrogon's labeling will include this risk in warnings and precautions as do other growth hormones.

5.2. Increased Risk of Neoplasm

In Study CP-4-004 OLE, one patient permanently discontinued the study as they developed an SAE of Schwannoma in OLE Year 2. Two patients in the somatrogon group developed skin tumors, and two patients in the Genotropin group developed skin tumors. In CP-4-006 OLE, one patient each in OLE years 2 and 3 experienced a benign skin neoplasm. As IGF-1 is a growth-promoting factor, increased IGD-1 levels may promote tumorigenesis. Growth hormone therapies address this class risk of developing neoplasms in warnings and precautions, as will the labeling for somatrogon.

5.3. Glucose Intolerance and Diabetes Mellitus

In CP-4-006, one patient in each OLE year 1 and 2 experience hyperglycemia. As GH products have antagonistic effects on insulin, this risk is included in all GH labels. Changes in glucose levels in somatrogon subjects were small with unknown clinical significance, and subjects remained

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

asymptomatic. This risk and the need to monitor glucose levels will be included in warnings and precautions as part of class labeling.

5.4. Intracranial Hypertension

There were no reports of intracranial hypertension in the somatrogon studies, and since headache is a common symptom, the reviewer team analyzed reports of headache. In Study CP-4-006's main phase, 17% of subjects using somatrogon reported a headache, while 22% of those using Genotropin reported headache. In Study CP-4-006, 4 subjects met the criteria for a fundoscopic exam (signs/symptoms of intracranial hypertension including persistent headaches or headache with nausea/vomiting that is not self-limited). None of these subjects had evidence of intracranial hypertension. As this remains a class risk, this will be included in warnings and precautions of somatrogon labeling.

5.5. Fluid Retention

Growth hormones are known to cause fluid and sodium retention, and somatrogon's safety data was reviewed for reports of edema, arthralgia, myalgia, and nerve compression. No cases were reported in the main phase of CP-4-006 in the somatrogon group, and there were 2 reports of myalgia in the Genotropin group. In CP-4-006 OLE year 2 3.4% of subjects using somatrogon reported arthralgia, and in OLE year 3, 1 subject using somatrogon reported arthralgia. No SAEs were reported, but this will be included in warnings and precautions as part of class labeling.

5.6. Hypoadrenalism

In Study CP-4-006's OLE, an SAE of adrenal insufficiency was reported, and was attributed by the clinical reviewer as exacerbation of preexisting insufficiency that was exacerbated by an acute infection.[13] Four subjects treated with somatrogon and 1 subject treated with Genotropin experienced adrenal insufficiency. Two subjects taking somatrogon in CP-4-006 experienced an episode of adrenal insufficiency in OLE years 2 and 3. No adrenal crises were reported, and most events were mild and resolved without drug discontinuation. Since growth hormones increase the conversion of cortisol to inactive cortisone, this class risk will be listed in warnings and precautions in somatrogon labeling.

5.7. Hypothyroidism

In Study CP-4-006, 9% of subjects treated with somatrogon and 10% of subjects treated with Genotropin had thyroid-related AEs. In OLE Year 2 of CP-4-006, 3.4% of subjects taking somatrogon, and in OLE year 3, 3% of subjects taking somatrogon experienced thyroid function impairment. This is unsurprising as treatment with GH products can bring to light subclinical or undiagnosed hypothyroidism. All subjects remained asymptomatic, and AEs were classified as mild to moderate. As this is a class risk, this will be listed in warnings and precautions of labeling.

5.8. Progression of Preexisting Scoliosis

In the first OLE period of CP-4-006, one patient reported a worsening scoliosis on Year 4 of somatrogon treatment as an SAE, and another reported a nonserious event of scoliosis. In OLE years 2 and 3 in CP-4-006, 6 subjects using somatrogon reported scoliosis. This is a known risk of GH therapies, and as with other GH products, will be listed in warnings and precautions of labeling.

5.9. Lipoatrophy

One subject using somatrogon in CP-4-006 in OLE Yea 1 reported atrophy at the injection site. This may occur if GH is injected into the same site over a long period of time. As with other GH products, this will be included in warnings and precautions of somatrogon labeling.

6. Expected Postmarket Use

Somatrogon is expected to be prescribed by endocrinologists and other specialists treating growth disorders. The prescribing population is likely familiar with the class-wide warnings and precautions and management of adverse events associated with somatrogon. These patients are regularly monitored by their practitioners to monitor effectiveness and safety of this therapy. Somatrogon will be administered as subcutaneous injection by patients or their caregivers.

7. Risk Management Activities Proposed by the Applicant

The applicant did not submit a REMS with this application, however, a proposed Risk Management Plan including an active surveillance long-term safety study in European patients was included.

7.1. Other Proposed Risk Management Activities

The Applicant has agreed to a Postmarketing Commitment to perform commercial shipping studies to qualify the actual shipping conditions for the prefilled pen.[12]

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of somatrogon on the basis of the efficacy and safety information currently available.[12]

Growth hormone deficiency is a serious illness diagnosed in childhood that has multiple negative implications that continue into adulthood. With somatrogon being injected once weekly, this new option is welcome to decrease injection site pain and potentially improved compliance versus products that are formulated for daily injections. Like multiple other marketed growth hormone products on the

market, the risks of somatrogon include increased mortality in acute illness and Prader-Willi Syndrome, serious hypersensitivity reactions, increased risk of neoplasm, glucose intolerance and diabetes mellitus, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis, progression of preexisting scoliosis, pancreatitis, and lipoatrophy. DRM and DGE considered these risks and if a REMS was necessary to mitigate them.

The safety concerns associated with somatrogon use are similar to other GH products and will be managed via warnings and precautions as other GH products do. These products have been used for decades, and we expect prescribers will be familiar with the risks and any necessary monitoring (such as glucose monitoring), that will be needed with another human growth hormone analogue. Many of the class-wide risks were observed in the pivotal study as either mild to moderate in severity, and some also resolved without drug discontinuation. After reviewing the additional data provided on ADA development in a majority of subjects using somatrogon, the clinical team could not find any negative effect of ADAs on efficacy or safety.

9. Conclusion & Recommendations

Based on the available data, DRM and DGE agree that a REMS is not necessary to ensure the benefits of somatrogon outweigh the risks, which will be managed via labeling. Should DGE have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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/s/

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Division of Risk Management (DRM)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761184
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Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D.
Review Completion Date	January 18, 2022
Subject	Defer comment on DRM evaluation of the need for a REMS for somatrogon-ghla
Established Name	somatrogon-ghla
Trade Name	Ngenla
Name of Applicant	Pfizer Ireland Pharmaceuticals
Therapeutic Class	human growth hormone
Formulation(s)	24 mg/1.2 mL (20 mg/mL); 60 mg/1.2 mL (50 mg/mL) Single-patient-use, disposable prefilled pen
Dosing Regimen	The recommended dose is 0.66 mg/kg body weight administered once weekly, on the same day each week, at any time of day.

This memo is to defer the Division of Risk Management (DRM) review of the need for a risk evaluation and mitigation strategy (REMS) for somatrogon-ghla, BLA 761184.

On October 22, 2020, the Applicant submitted BLA 761184 with the proposed indication (b) (4) The submission included draft labeling and did not include a REMS. On December 10, 2021 The Division of General Endocrinology (DGE) issued a "Deficiencies Preclude Discussion" letter due to deficiencies that were identified during the review of this application that preclude discussion of labeling and postmarketing requirements/commitments at this time.[1]

The DGE clinical reviewer recommends Complete Response (CR) for regulatory action based on immunogenicity effects that may decrease the efficacy and potentially affect the long-term safety of somatrogon, and development of anti-carboxy terminal peptide (anti-CTP) antibodies that may interfere with human chorionic gonadotropin (hCG)-based diagnostic assays.[2] In addition, the Office of Pharmaceutical Quality (OPQ) is recommending a CR because inspection of the Applicant's manufacturing facilities in Belgium were not completed due to restrictions in travel.[2] Please refer to DGE's Integrated Review[2] for a detailed review of identified issues for this BLA and recommendations that will be sent to the Applicant. The following information is a summary of the conclusions in the Integrated Review that recommends CR[2:]

> *Somatrogon increased annualized growth velocity (AGV) at the end of a 12-month treatment period and was shown to be non inferior to Genotropin, although not superior to Genotropin. In general, this efficacy finding in a new human growth hormone (hGH) formulation could support the benefit of the product for the proposed indication. However, reliance on one-year data presupposes the absence of factors, such as immunogencity, that may offset growth and affect final adult height. The immunogenicity of somatrogon is unusally high; the data included in the BLA demonstrated that treatment with somatrogon was associated with a high and persistent incidence of antidrug antibodies (ADA) comared to Genotropin. Furthermore, nearly all (76%) ADA-positive subjects had persistent antibodies in the somatrogon group versus 5% of ADA-positive subjects in the Genotropin group. Concerningly, five subjects developed neutralizing antibodies. Therefore, the effect on long-term growth in these children remains unknown, i.e. cannot be assumed to track with AGV over only one year, because the high immunogenicity rate can potentially attenuate subsequent growth and negatively impact potential improvement in final adult height. There is also concern for patients who are treated with somatrogon and later switch to hGH treatment. If these patients develop persistent neutralizing antibodies while being treated with somatrogon, other hGH products may be rendered ineffective when they are treated later.*
>
> *The 12-month safety profile of somatrogon was generally consistent with the drug class. The presence of antibodies was not associated with higher rates of adverse events, including hypersensitivity, compared to Genotropin during the one-year randomized period. However, the high and persistent rate of ADA represents a risk for a detrimental effect of these antibodies on the long-term safety of the drug.*
>
> *There is also a concern with the development of anti-CTP antibodies. A total of 11 subjects in the clinical program had positive anti-CTP antibodies. The potential risks of anti-CTP*

antibodies are interference with the hCG-based diagnostic assays (e.g., pregnancy test, ovarian cancer) and risk of adverse outcomes on fertility and pregnancy. These risks remain unknown due to scarcity of clinical data on incidence and potential risks of circulating anti-CTP antibodies. An assessment is necessary to ensure that an adequate informed risk:benefit determination can be made in female adolescents who may be sexually active.

Based upon review of all available efficacy and safety data, the benefits of somatrogon do not outweigh the risks. There are other hGH products with low immunogenicity and well-characterized efficacy and safety in the US market, including a once-weekly formulation. The unusually high immunogenicity introduces potential impacts on efficacy and safety that are not associated with the approved products. The potential effect of ADA including neutralizing antibodies on growth attenuation during the treatment with somatrogon beyond 12 months and ultimately on final adult height remains unknown due to the lack of long-term data. Lastly, the impact of ADA on efficacy of other hGH formulations when the patient is switched to the treatment with other hGH products (as adult or due to growth/safety concerns) also remains unknown.

A better understanding of whether ADA, including neutralizing antibodies, have an impact on longer-term efficacy is needed to fully assess the risk from immunogenicity. It is also important to understand the fate of neutralizing antibodies as well as the factors that may potentially mitigate their persistence, such as drug discontinuation and switching to other hGH formulations. A better understanding of the product- or device-related factors that are leading to the high immunogenicity would also be important should the Applicant seek to reformulate or redesign.

An inspection of Pfizer Manufacturing Belgium NV facility is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel to Belgium, we were unable to complete an inspection during the current review cycle for your application. You may respond to the other deficiencies in this Complete Response letter while the travel restrictions remain in effect. However, even if all other deficiencies are addressed, the application cannot be approved until the required FDA inspection is completed and the findings are assessed with regard to your application.

Based on this information, an evaluation of the need for a REMS for somatrogon-ghla will be undertaken by DRM after the Applicant addresses the deficiencies in the CR letter. Please send DRM a new consult request at such time. This memo serves to close the existing consult request to DRM for somatrogon-ghla under BLA 761184.

References

[1] Deficiencies Preclude Discussions Letter, dated December 10, 2021. [Reference ID: 4902998]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed January 7, 2022.

[2] DGE Integrated Review (draft) for somatrogon-ghla, BLA 761184, dated January 14, 2021.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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