Taiwan Food and Drug Administration

Assessment Report

Trade Name：能增樂預填充注射筆 24 毫克/ NGENLA 24 mg solution for injection in prefilled pen
能增樂預填充注射筆 60 毫克/ NGENLA 60 mg solution for injection in prefilled pen

Active Ingredient：Somatrogon

License Number：MOHW-BI 001196
MOHW-BI 001197

Applicant：美商惠氏藥廠（亞洲）股份有限公司台灣分公司

Approval Date：2022.8.5

Indication：
適用於治療因生長激素分泌不足導致生長障礙之兒童病人。
Treatment of pediatric patients with growth disturbance due to insufficient secretion of growth hormone.

Background Information

Trade Name	能增樂預填充注射筆 24 毫克/ NGENLA 24 mg solution for injection in prefilled pen 能增樂預填充注射筆 60 毫克/ NGENLA 60 mg solution for injection in prefilled pen
Active Ingredient(s)	Somatrogon
Applicant	美商惠氏藥廠（亞洲）股份有限公司台灣分公司
Dosage Form & Strengths	注射液劑 24 mg、60 mg
Indication	適用於治療因生長激素分泌不足導致生長障礙之兒童病人。 Treatment of pediatric patients with growth disturbance due to insufficient secretion of growth hormone.
Posology	詳細內容請參閱仿單 Please refer to the approved package insert.
Pharmacological Category **ATC Code**	H01AC08

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Somatrogon is a long-acting recombinant human growth hormone produced in Chinese hamster ovary cells. It is comprised of the amino acid sequence of human growth hormone with one copy of the C-terminal peptide (CTP) from the beta chain of human chorionic gonadotropin at the N-terminus and two copies of CTP at the C-terminus. The CTP domains with multiple O-linked glycosylation sites account for an extended half-life of somatrogon which allows for weekly dosing.

The description of manufacturing process and process controls is considered adequate. The overall control strategy including control of raw materials, manufacturing process and adventitious agents is sufficient to ensure process performance and the quality of somatrogon. The structure and characteristics of somatrogon have been determined using appropriate analytical approaches. Process-related impurities and product-related impurities are well-controlled. The release tests for somatrogon are acceptable. Batch release data adequately demonstrate the consistency of the manufacturing process capabilities. A two-tiered system for commercial somatrogon reference material has been implemented. The container closure system is acceptable. The real time data provided are adequate to support the proposed drug substance shelf life.

2.1.2 Drug product

The somatrogon drug product, NGENLA, is presented as a single-patient-use, disposable prefilled pen designed for subcutaneous injection. The prefilled pen consists of a 3 mL Type I clear glass cartridge containing colorless to slightly light yellow drug product solution at concentrations of 24 mg/1.2 mL (20 mg/mL) or 60 mg/1.2 mL (50 mg/mL). The drug product solution is formulated using compendial excipients including m-Cresol as preservative.

Details of formulation development and manufacturing process development are provided. The drug product solution manufacturing process is sufficiently controlled to ensure consistent production of drug product solution lots of the intended quality. The release and stability specifications for somatrogon drug product solution are acceptable. Leachable study assessment is provided to ensure safety for the use of the container closure system. The stability data currently available for somatrogon drug product solution are adequate to support the proposed shelf life of 24 months at 5±3 °C and functional performance of the pen through to 24 months when stored at 5±3 °C, with an in-use period of 28 days during the shelf life.

In summary, the information on the drug substance and drug product was provided and the quality of NGENLA is considered acceptable.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Somatrogon is a drug for the treatment of pediatric patients with growth disturbance due to insufficient growth hormone secretion. Somatrogon is a single-chain polypeptide that is composed of the amino acid sequence of human growth hormone (hGH) and 1 copy of C-terminal peptide (CTP) from the β-chain of human chorionic gonadotropin (hCG) at the N-terminal and 2 copies at the C-terminal. The *O*-glycans in the CTP are expected to extend the half-life of somatrogon.

Somatrogon binds to the growth hormone receptor and initiates a signal transduction cascade to increase the insulin-like growth factor-1 (IGF-1) to improve growth and metabolism. The *in vitro* pharmacology studies compared the binding affinity between somatrogon and recombinant human growth hormone in rats, rhesus monkeys, and humans. Somatrogon stimulated the proliferation of cells expressing human growth hormone receptors.

The *in vivo* pharmacology studies indicated that somatrogon increased body weight gain in both rats and monkeys and increased IGF-1 response in hypophysectomized rats. The safety pharmacology endpoints were evaluated in the pivotal repeated-dose toxicity studies in rats

and monkeys. No significant effects of somatrogon on CNS, cardiovascular, and respiratory systems were observed.

2.2.2 Toxicological Studies

The pivotal repeated-dose toxicity studies included a 4-week study in rats and a 26-week study in rhesus monkeys. Because of their age at first dose, the monkeys can be considered juvenile animals. In these studies, somatrogon did not induce significant adverse effects. Anti-drug antibodies were observed in most animals but had little neutralizing effects and did not affect IGF-1 response. Based on the ICH S6(R1) guideline, a 26-week repeated-dose toxicity study could support the marketing of a biotechnology-derived pharmaceutical.

Genotoxicity and carcinogenicity studies were not conducted since somatrogon is a protein-based drug that is used as replacement therapy. Somatrogon exhibited no significant effects on reproductive performance and fetal development. The teratogenicity study was only conducted in rats, which is acceptable since the patient population is children rather than adults. The pharmaceutical effects of increasing body weight and food consumption were observed in both parental and filial generations. Local tolerance was evaluated in the pivotal toxicity studies. Mild and reversible local response presented at the injection sites.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

In target pediatric patients, somatrogon showed dose-proportional manner following subcutaneous doses of 0.25, 0.48, and 0.66 mg/kg/week. There is no accumulation after once weekly administration.

According to population pharmacokinetic analysis (PopPK) in target pediatric patients, somatrogon serum level increased slowly, peaking 6~18 hours post dose. The $C_{max,ss}$ and AUC_{ss} following 0.66 mg/kg/week were 650 ng/mL and 20300 ng*hr/mL, respectively. Somatrogon was expected to be primarily degraded by proteolytic catabolism. The PopPK estimated apparent clearance and central volume of distribution were 0.0325 L/hr/kg and 0.716 L/kg, respectively. The effective $T_{1/2}$ was 28.3 hours.

Patients who tested anti-drug antibody positive had an approximately 25.8% decrease in apparent clearance, leading to 45% increase in somatrogon steady-state average concentration.

In pediatric clinical trials, somatrogon increased IGF-1. The peak IGF-1 level occurred at 48 hours post dose and declined to baseline at 168 hours post dose. 96 hours post dose was identified as the most appropriate timepoint for measurement of IGF-1.

The exposure of somatrogon decreases with an increase in body weight. Simulation report predicted that the exposure in a subject weighting 55 kg to be 69.5% of what would be expected for a 15 kg subject (14797 ng*hr/mL vs. 21290 ng*hr/mL).

2.3.2 Interaction Studies

No drug-drug interaction studies have been performed with somatrogon. It was known to induce CYP3A4 mRNA expression in vitro. The clinical impact is still unknown.

Several pharmacodynamic interactions were noticed, including oral oestrogen therapy, glucocorticoid, insulin, hypoglycaemic drugs and thyroid replacement therapy. Growth monitoring and dose adjustment of somatrogon or the concomitant drug may be required.

2.3.3 Special Populations

No dedicated hepatic or renal impairment study was conducted. No dose recommendation can be made.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A pivotal study (study ID number: CP-4-006) was provided to support the claim of somatrogon (MOD-4023) for growth hormone deficiency (GHD) in pre-pubertal children. CP-4-006 is a phase 3, randomized, open-label, active-controlled, parallel-group study to demonstrate that somatrogon SC (0.66 mg/kg/wk, subcutaneous) administration in prepubertal children with GHD is clinically non-inferior to Genotropin (0.034 mg/kg/day).

Primary endpoint is designated as annual HV (height velocity) in cm/year at 12 months. Primary efficacy analysis is to demonstrate that weekly somatrogon is non-inferior to daily Genotropin by a non-inferiority (NI) margin of 1.8 cm/year, where ANCOVA model is applied with predictor variables X, such as classification terms for treatment group, gender, 3 randomization stratification factors (Region, Age, GH levels), and baseline height SDS, to fit the outcome Y (i.e., annual HV).

A total of 536 subjects were screened, of whom 224 were finally randomized in a 1:1 ratio to the somatrogon (N = 109) or Genotropin (N = 115) treatment groups. Patients enrolled were pre-pubertal children with median age of 7.87 years and approximate 60% above the age of 7 years. Nearly 75% belong to white. Most of the population are male (~72%).

In the CP-4-006 trial, the primary endpoint was met. When comparing annualized HV after 12 months of treatment (mean difference = 0.33, 95% CI: -0.24 to 0.89), the lower bound of

95% CI is within the pre-specified margin (i.e., -1.8 < -0.24). Additional sensitivity/subgroup analyses also showed consistency with the primary analysis.

2.4.2 Safety Results

Major adverse events include injection site reactions (pain, erythema, rash), immunogenicity, headache, pyrexia, vomiting and arthralgia.

Growth hormone increases the extrathyroidal conversion of T4 to T3 and may unmask incipient hypothyroidism. Patients with pre-existing hypothyroidism should be treated accordingly prior to the initiation of treatment with somatrogon as indicated.

2.5 Bridging Study Evaluation

The ethnic sensitivity of somatrogon was evaluated based on data from East Asian pediatric population with growth hormone deficiency (GHD). The PK parameters of somatrogon was impacted significantly by body weight, age and the presence of anti-drug antibody (ADA).

Korean pediatric GHD population showed lower absorption extent of somatrogon by 26~36% as compared to non-East Asian pediatric GHD population in the same study. In a cross-study comparison, the elimination rate of Japanese pediatric GHD population was 44~47% lower than that of non-Japanese pediatric GHD population, but their absorption extent was similar.

The incidence rate of ADA-positive in Japanese and Korean pediatric population was higher than that in Non-East Asian pediatric population. And population PK analysis has indicated that ADA-positive decreased clearance by 25.8% and increased somatrogon $C_{avg,ss}$ by 45%.

The ethnic sensitivity might be contributed from body weight, age, ADA or ethnic difference among Asians. Even though, the ethnic sensitivity on the PK was acceptable considering the moderate inter-subject variation (~60%) and body-weight adjusted dosing regimen of somatrogon.

Efficacy and safety results of East Asians derived from the Japanese Phase III Study CP-4-009 (22 subjects of somatrogon group and 22 subjects of genotropin group) and subgroup analysis of 14 (6%) East Asians (Taiwan and Korea) of Study CP-4-006. The results of efficacy and safety of East Asians are acceptable.

2.6 Conclusion

Efficacy was demonstrated for somatrogon by a phase 3, randomized, open-label, active-controlled, parallel-group study in prepubertal children with GHD. The safety profile was acceptable. Approval of somatrogon for treatment of pediatric patients with growth disturbance due to insufficient secretion of growth hormone is recommended.

3. Post-Marketing Requirements

Post-authorization non-interventional surveillance study for effectiveness and safety including neoplasms and Type 2 DM risk is required.