This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Report on Investigation Results

March 2, 2022

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Somatropin (genetical recombination)
[Brand name]	See Appendix I
[Indications]	See Appendix I
[Dosage and administration]	See Appendix I
[Approval holder]	See Appendix I
[Investigating office]	Office of Pharmacovigilance I

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II. Investigation background

Somatropin (genetical recombination) is a recombinant human growth hormone preparation, and the drugs described in Appendix 1 (hereinafter referred to as “somatropin preparations”) were approved for marketing (hereinafter referred to as “approved”) with the indications for growth hormone-deficient short stature without epiphyseal closure, etc. (refer to Appendix 1 for details) The first somatropin preparation approved in Japan is Genotropin (4IU), which was approved in 1988. Also, Somapacitan (genetical recombination) (Brand name: Sogroya Subcutaneous Injection 5 mg, 10 mg, hereinafter referred to as “Somapacitan”), which is a long-acting human growth hormone analogue, was approved on January 22, 2021.

Because growth hormone (hereinafter referred to as “GH”) has anti-insulin-like effects, administration of all somatropin preparations to patients with diabetes mellitus has been contraindicated from the time of initial approval.

On March 10, 2021, a request to ask for deleting the patients with diabetes mellitus from contraindication, the Request for the Revision of Package Insert in which Somatropin (genetical recombination) is Contraindicated in Patients with Diabetes Mellitus, was submitted to Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as the “Pharmaceutical Safety Division”) from the Japan Endocrine Society and the Japanese Society for Pediatric Endocrinology because of the reasons including that the patients with diabetes mellitus cannot receive the benefits by somatropin preparations due to the above contraindication in Japan.

The following are described in the request as the reasons for not requiring a contraindication for administration of somatropin preparations to the patients with diabetes mellitus.

(1) It has been reported (Clin Endocrinol 2006; 64: 444-9) that treatment with somatropin preparations may improve insulin resistance in the long term in patients with type 2 diabetes mellitus with inadequate glycaemic control.

(2) Although the American Endocrine Society guideline (J Clin Endocrinol Metab 2011; 96: 1587-609) states that higher doses of antidiabetic drugs may be required due to the administration of somatropin preparations, the guideline does not contraindicate administration in patients with diabetes mellitus.

(3) It has been reported (J Jpn Pediatr Soc 1996; 100: 877-81, Int J Mol Sci 2019; 20: 77, Horm Res Paediatr 2014; 82: 53-8, Int J Mol Sci 2019; 20: 772) in several cases that in patients with type 1 diabetes mellitus, somatropin preparations could be administered with well-controlled diabetes mellitus by appropriately adjusting the dose of insulin.

(4) The package inserts of the EU, US and Australia do not contraindicate administration of somatropin preparations to patients with diabetes mellitus, subjecting such administration to special caution.

(5) For Somapacitan, no safety concerns that require contraindicating patients with diabetes mellitus were identified in the phase III study. The drug is not contraindicated in patients with diabetes mellitus.

On December 21, 2021, the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the PMDA) in response to the request from the Pharmaceutical Safety Division under the “Notification Request of Investigation Related to the Safety of Drugs, etc.” (PSEHB/PSD 1221 No.1) conducted an investigation on the safety of administration of somatropin preparations to patients with diabetes mellitus as follows.

PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. PMDA Investigation

1. Background of the current contraindication in patients with diabetes mellitus

PMDA referred to the approval holders for how the drug was contraindicated in patients with diabetes mellitus and the holders responded as follows:

It was found that, in 1974 when a pituitary-derived human growth hormone preparation (hereinafter referred to as “p-hGH preparation”) was granted a license for import and marketing, the Precaution section of the package insert noted, with no information on the background of the contraindication, that “This drug should not be administered to patients with diabetes mellitus.” Afterwards, in 1988 when a somatropin preparation (brand name: Genotropin (4 IU)) was granted a license for import and marketing, the

CONTRAINDICATIONS section listed “Patients with diabetes mellitus” in the package insert, with no details on how patients with diabetes mellitus were listed as a contraindication apart from falling in line with the p-hGH preparation.

Meanwhile, the marketing authorization holder of Norditropin replied that the anti-insulin-like effects of p-hGH presumably were the basis for the contraindication. However, no specific information was found on how and why administration in patients with diabetes mellitus was contraindicated for somatropin preparations including other products than Genotropin.

2. Current description related to administration of somatropin preparations in patients with concurrent diabetes mellitus or risk factors of diabetes mellitus (such as obesity and family history) in the Japanese and overseas clinical practice guidelines, overseas package inserts, and Japanese and overseas standard textbooks

2.1 Japanese and overseas clinical practice guidelines

Japanese and overseas guidelines state the following:

(1) American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care [1] (edited by American Association of Clinical Endocrinologists and American College of Endocrinology Growth Hormone Task Force 2019, hereinafter referred to as the “American Association of Clinical Endocrinologists and American College of Endocrinology (AACE) Guidelines (2019)”)

Regarding the administration of somatropin preparations to patients with adult growth hormone deficiency (hereinafter referred to as "AGHD") with concurrent diabetes mellitus and patients who developed growth hormone deficiency (hereinafter referred to as "GHD") in childhood and concurrent with diabetes mellitus transitioning to adulthood, the guidelines state the following:

- In patients with concurrent diabetes mellitus or previous gestational diabetes mellitus, it is recommended to start somatropin preparations at low doses (0.1 to 0.2 mg/day).
- Longer time intervals and smaller dose increments of somatropin preparations may be necessary.

[1] Endocr Pract 2019; 25: 1191-232

- If pre-existing diabetes mellitus worsens while on somatropin preparations therapy, it is strongly recommended to initiate or increase the doses of antidiabetic therapy or discontinue the somatropin preparations therapy and optimize treatment of diabetes mellitus before considering resuming the therapy.
- Active proliferative or severe nonproliferative diabetic retinopathy is contraindicated.

(2) Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline[2] (The Endocrine Society Clinical Practice Guideline)

Regarding the GH treatment with patients with AGHD and concurrent diabetes mellitus, the guidelines state the following:

- GH treatment in patients with concurrent diabetes mellitus may require adjustments in antidiabetic drugs for the following reasons.
  - In a clinical trial of GH treatment, it has been reported (Clin Endocrinol (Oxf) 1998; 48: 795-802) that several patients developed insulin resistance and type 2 diabetes mellitus in the early stages of treatment.
  - There is considerable variability in changes in insulin sensitivity due to differences in body composition, age, and genetic predisposition.
  - In a clinical trial (J Clin Endocrinol Metab 2004; 89: 2048-56) designed to evaluate the effectiveness, etc. of GH treatment in patients with AGHD, significantly more patients developed impaired glucose tolerance in the GH treatment group compared with the placebo group.

(3) Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: A statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia[3] (Growth Hormone Research Society, 2007 hereinafter referred to as the "GRS Consensus Guidelines")

The consensus guidelines of Growth Hormone Research Society (hereinafter referred to

[2] J Clin Endocrinol Metab 2011; 96: 1587-609
[3] Eur J Endocrinol 2007; 157: 695-700

as the "GRS"), in which the Japan Endocrine Society participates, state the following:

- Increased knowledge of GH physiology has led to dose adjustments that have substantially reduced the incidence of side effects, and GH is now recognized as a safe therapy insofar as standards of care are followed.
- GH replacement therapy is not associated with an increased incidence of type 1 and type 2 diabetes mellitus. However, it can increase insulin resistance and sometimes worsen glucose tolerance. Thus, individuals predisposed to type 2 diabetes mellitus, such as those with a positive family history, or who are obese or older, require careful glycaemic monitoring. If type 2 diabetes mellitus is diagnosed, it should be managed similarly to any other patient with this disease, and GH replacement therapy continued.

(4) 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[4] (The Drug and Therapeutics and Ethics Committees of the Pediatric Endocrine Society, 2016)

The Guidelines state that since it has been reported (J Clin Endocrionol Metab 1997; 82: 3234-8) that carbohydrate metabolism is altered during GH therapy of children with either isolated growth hormone deficiency or idiopathic short stature, children with type 1 diabetes mellitus will require higher doses of insulin if/when concurrently treated with GH.

(5) Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease[5] (the European Society for Paediatric Nephrology CKD–Mineral and Bone Disorder, Dialysis and Transplantation working groups 2019, hereinafter referred to as the "European Society for Paediatric Nephrology (ESPN) Guidelines")

The Guidelines state that GH must not be started in patients with inadequately controlled diabetes mellitus and GH is contraindicated in patients with active proliferative or severe nonproliferative diabetic retinopathy.

(6) Growth Hormone Research Society Workshop Summary: Consensus Guidelines

[4] Horm Res Paediatr 2016; 86: 361-97
[5] Nat Rev Nephrol 2019; 15: 577-89

for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome[6] (**Growth Hormone Research Society, 2013)**

Regarding the GH treatment in patients with Prader-Willi syndrome complicated by diabetes mellitus, the Guidelines state the following:

- In patients with inadequately controlled diabetes mellitus, it is recommended not to initiate GH treatment.
- Product labeling information for GH preparations lists active proliferative or severe nonproliferative diabetic retinopathy as contraindication.
- Because treatment with GH decreases insulin sensitivity, inadequately controlled diabetes mellitus, regardless of the presence or absence of diabetic complications, such as retinopathy, demands attention before initiation of GH therapy in patients with PWS.

(7) Guide for Diagnosis and Treatment of Hypothalamic and Pituitary Impairment 2018 edition[7] **(The Japan Endocrine Society, 2018)**

The contraindication of GH therapy in patients with diabetes mellitus is noted.

(8) Others

PMDA investigated the Japanese and overseas clinical practice guidelines listed below, finding none of them mentioning administration of somatropin preparations to patients with concurrent diabetes mellitus.

- Guideline for the management of Noonan Syndrome[8] (Shropshire Community Health NHS Trust, 2020)
- Guideline for management of Prader Willi Syndrome in children and young people[9] (Shropshire Community Health NHS Trust, 2020)
- Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting[10] (the 2016 Cincinnati International Turner Syndrome Meeting, 2017)
- The Investigation and Management of the Small-for-Gestational-Age Fetus[11] (Royal

[6] J Clin Endocrinol Metab 2013; 98: E1072-87
[7] Folia endocrinologica Japonica 2019; 95: 1- 60
[8] https://www.shropscommunityhealth.nhs.uk/content/doclib/11703.pdf (accessed on December 27, 2021)
[9] https://www.shropscommunityhealth.nhs.uk/content/doclib/11499.pdf (accessed on December 27, 2021)
[10] Eur J Endocrinol 2017; 177: 1-70
[11] https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_31.pdf (accessed on 27, December, 2021)

College of Obstetricians and Gynaecologists, 2014)

- Guidelines for the Transition from Childhood Growth Hormone Treatment to Adult Growth Hormone Treatment in Growth Hormone-deficient Short Stature[12] (growth hormone committee in the Japanese Society for Pediatric Endocrinology, 2006)
- Guideline for GH Treatment in Short Stature in Patients Born Small-for-gestational Age (hereinafter referred to as "SGA")[13] (growth hormone committee by the Japanese Society for Pediatric Endocrinology, the committee on pharmaceutical affairs by the Japan Society for Premature and Newborn Medicine, 2007)
- Precautions for Implementation of GH Treatment in Short Stature with Noonan Syndrome[14] (the Japanese Society for Pediatric Endocrinology, 2020)
- Treatment Guideline for Achondroplasia[15] (the committee for preparation of Treatment Guideline for Achondroplasia of the research project of Building Treatment Network of Skeletal Dysplasia Aiming at Formulating Treatment Guideline as Practical Implementation Project of Intractable Disease by Japan Agency for Medical Research and Development, 2019)
- CKD Clinical Practice Guide for Puberty and Adolescent Patients[16](the investigation team of Intractable Renal Disease in the Research Project to Conquer Intractable Disease by MHLW, 2016)

2.2 Current description of overseas package inserts

The current description of overseas package inserts of somatropin preparations concerning administration to patients with concurrent diabetes mellitus was as follows (see Appendix 2 for details):

(1) The US package insert

- It is described in the Contraindications section that somatropin preparations are contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy. Administration to patients with diabetes mellitus is not contraindicated.
- It is alerted in the Warnings and Precautions section that glucose levels should be monitored periodically in all patients treated with somatropin preparations, especially in

[12] J Jpn Pediatr Soc 2006; 110: 109-13
[13] J Jpn Pediatr Soc 2007; 111: 641-6
[14] http://jspe.umin.jp/medical/files/guide20200917.pdf (accessed on 27, December, 2021)
[15] Http://jspe.umin.jp/medical/files/guide2_20190111.pdf (accessed on 27, December, 2021)
[16] Jpn J Nephrol 2016; 58: 1095-233

those with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus. It is also described that patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin preparations therapy and that the doses of antihyperglycemic drugs may require adjustment when somatropin preparations therapy is instituted in these patients.

- It is stated in the Drug Interactions section that the dose of insulin and/or other antihyperglycemic drugs may require adjustment when somatropin preparations therapy is initiated in patients with diabetes mellitus requiring drug therapy.

(2) The EU package insert

- 3 somatropin preparations have been approved, and each preparation has different descriptions for precautions.
- There is no description concerning patients with diabetes mellitus in the Contraindications section (common in 3 preparations).
- The following are stated in the Special warnings and precautions for use section.
  - It is recommended to measure fasting insulin and blood glucose before the start of treatment and annually thereafter in Turner syndrome (brand name: Norditropin) and SGA children (common in 3 preparations).
  - In patients with increased risk for diabetes mellitus (e.g., familial history of diabetes mellitus, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed (common in 3 preparations).
  - If overt diabetes mellitus occurs, growth hormone should not be administered (brand name: Genotropin, Norditropin).
  - If overt diabetes mellitus occurs, growth hormone should not be administered until the patient has been stabilized for diabetes mellitus care (brand name: Humatrope).
  - For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin preparations therapy is instituted (common in 3 preparations).
  - Patients with impaired glucose tolerance or diabetes mellitus should be closely monitored during administration of somatropin preparations (common in 3 preparations).
- It is described in the Interaction with other medicinal products and other forms of

interaction section that patients with diabetes mellitus who receive concomitant somatropin preparations may require adjustment of their doses of insulin and/or other anti-hyperglycaemic agents (common in 3 preparations).

(3) Canadian package insert

- 3 somatropin preparations have been approved, and each preparation has different descriptions for precautions.
- It is described in the Contraindications section that somatropin preparations are contraindicated in the following patients. Administration to patients with diabetes mellitus is not contraindicated for each preparation.
  - Patients with proliferative or preproliferative diabetic retinopathy (brand name: Norditropin)
  - Patients with active proliferative or severe nonproliferative diabetic retinopathy (brand name: Genotropin, Humatrope)
  - Patients with Prader-Willi syndrome who have inadequately controlled diabetes mellitus (brand name: Genotropin)
- The following are stated in the Warnings and Precautions section.
  - Patients with diabetes mellitus or glucose intolerance should be monitored closely during therapy with somatropin preparations, as an adjustment of their antidiabetic therapy may be required (common in 3 preparations).
  - Treatment with somatropin preparations may decrease insulin sensitivity in patients with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus, as well as in those receiving high dose corticosteroid therapy or with impaired glucose tolerance. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin preparations treatment. Therefore, patients who receive somatropin preparations should be monitored for evidence of abnormal glucose metabolism and/or diabetes mellitus (common in 3 preparations).
  - Therapy with somatropin preparations should be excluded for pediatric patients with Prader-Willi syndrome who have inadequately controlled diabetes mellitus(brand name: Genotropin).
  - Patients with pre-existing type 1 or type 2 diabetes mellitus or impaired glucose

tolerance should be monitored closely during somatropin preparations therapy. The doses of antihyperglycemic drugs may require adjustment when somatropin preparations therapy is instituted in these patients (brand name: Norditropin).

- The following are stated in the Drug Interactions section.
  - It is described that the dose of insulin and/or other anti-hyperglycemic agents may require adjustment when somatropin preparations therapy is initiated in patients with diabetes mellitus requiring drug therapy (brand name: Genotropin, Norditropin).
  - It is stated that patients with diabetes mellitus who receive concomitant somatropin preparations may require adjustment of their doses of insulin and/or other antihyperglycemic agents(brand name: Humatrope).

(4) Australian package insert

- 3 somatropin preparations have been approved, and each preparation has different descriptions for precautions.
- It is described in the Contraindications section that somatropin preparations are contraindicated in the following patients. Administration to patients with diabetes mellitus is not contraindicated for each preparation. Administration of Genotropin is not contraindicated in patients with diabetic retinopathy as well.
  - Patients with proliferative or preproliferative diabetic retinopathy (brand name: Norditropin) .
  - Patients with active proliferative or severe nonproliferative diabetic retinopathy (brand name: Humatrope) .
- The following are stated in the Special warnings and precautions for use section.
  - Somatropin preparations reduce insulin sensitivity, and therefore patients should be observed for evidence of glucose intolerance (brand name: Genotropin, Humatrope).
  - Patients with diabetes mellitus who receive concomitant somatropin preparations may require adjustment of their doses of insulin and/or other anti-hyperglycaemic agents (brand name: Genotropin, Humatrope).
  - In SGA children it is recommended that fasting insulin and blood glucose be measured before the start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus, OGTT should be performed. If overt diabetes

mellitus occurs, growth hormone should not be administered (brand name: Norditropin, Humatrope).

- It is described in the Interactions with other medicines and other forms of the interactions section that patients with diabetes mellitus who receive concomitant somatropin preparations may require adjustment of their doses of insulin and/or other anti-hyperglycaemic agents (brand name: Genotropin, Humatrope).

2.3 Japanese and overseas standard textbooks

Harrison's Principles of Internal Medicine (Jameson JL. et al, 2018) states the following, regarding GH therapy in patients with AGHD.

- Administration of GH is contraindicated in patients with inadequately controlled diabetes mellitus or retinopathy.
- Because of the anti-insulin-like effects of GH, administration to patients on insulin requires close monitoring for dose adjustment. In patients with type 2 diabetes mellitus, an increased insulin resistance is observed during the initial administration period. In the long term, however, with abdominal fat decreased in line with GH treatment, glycaemic control usually improves.

In the Latest Endocrinology and Metabolism, which is the relevant Japanese standard textbook (Shindan to Chiryo sha, 2013), administration of somatropin preparations to patients with concurrent diabetes mellitus is not mentioned.

3. Current description of the precautions for somatropin preparations in Japan

Administration of somatropin preparations is contraindicated in patients with concurrent diabetes mellitus based on the anti-insulin-like effects of GH.

4. Adverse reactions reports

4.1 Serious cases of adverse reactions in patients with concurrent diabetes mellitus in Japan

Of the cases of adverse reactions that the approval holder collected in Japan between the time of approval of somatropin preparations and December 21, 2021, 21 events were serious

and developed in 16 cases with concurrent diabetes mellitus[17].

The 21 events were: 4 events in 4 cases of diabetes mellitus, 3 events in 3 cases of type 2 diabetes mellitus, 1 event in 1 case each of diabetic ketosis, hyperglycaemia, death, myocardial infarction, essential thrombocythaemia, hydrocephalus, recurrent pituitary tumour, benign pituitary tumour, adenocarcinoma of colon, decreased appetite, fatigue, insomnia, seizure, and loss of control of legs (Appendix 3). In the PMDA's evaluation, a causal relationship between the adverse reaction and somatropin preparation was considered to be reasonably possible in 1 case of type 2 diabetes mellitus (Appendix 3, No. 5).

Of the 8 cases in which adverse reactions related to glucose metabolism[18] of diabetes mellitus, type 2 diabetes mellitus, diabetic ketosis, or hyperglycaemia were observed, 5 cases were improved or resolved with temporal discontinuation of somatropin preparations or initiation of antidiabetic drugs, with the outcomes of the remaining 3 cases unknown.

One event in 1 case each of death and myocardial infarction led to death. No cases resulted in death by worsened glycaemic control[19].

4.2 Non-serious cases of adverse reactions in patients with concurrent diabetes mellitus in Japan

Among the cases of adverse reactions that the approval holders collected in Japan between the time of approval of somatropin preparations and December 21, 2021, 15 cases with concurrent diabetes mellitus[17] developed 23 non-serious events.

Of the 23 events in 15 cases, 12 events in 11 cases were adverse reactions related to glucose metabolism[18], which were: 4 events in 4 cases each of increased blood glucose and diabetes mellitus, 1 event in 1 case each of increased glycohaemoglobin, insulin resistance, inadequately controlled diabetes mellitus, and obesity (see Appendix 4). In the PMDA's evaluation, a causal relationship between the adverse reaction related to glucose metabolism and somatropin preparation was reasonably possible in 1 event in 1 case of inadequately controlled diabetes mellitus (Appendix 4, No. 8), which was resolved with initiation of an antidiabetic drugs.

[17] The patients were those with a description of "diabetes mellitus" in the column of "underlying diseases/complications/past history."
[18] The events corresponded to the adverse reactions falling under SMQ "Hyperglycaemia/ new onset diabetes mellitus (broad scope terms)".
[19] The case whose outcome was death and who fell under SMQ "Hyperglycaemia/ new onset diabetes mellitus (broad scope terms)"

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4.3 Serious cases of adverse reactions in patients with concurrent diabetes mellitus overseas

Regarding the cases of adverse reactions that the approval holders collected overseas between the time of approval of somatropin preparations and December 21, 2021, no cases led to death due to worsened glycaemic control[19] among those of serious adverse reactions that developed in patients with concurrent diabetes mellitus[17].

5. Published literature

The following 8 published articles were retrieved [20] which were clinical trials, epidemiological studies, or case reports on the safety of administration of somatropin preparations to patients with concurrent diabetes mellitus .

5.1 Efficacy of Growth Hormone Treatment in Children with Type 1 Diabetes Mellitus and Growth Hormone Deficiency – An Analysis of KIGS Data (J Pediatr 2018; 198: 260-4)

A cohort study was conducted to analyze the response to GH treatment and GH doses in pediatric GHD patients with type 1 diabetes mellitus by using the KIGS database which is the Pfizer International Growth Database. As pediatric GHD patients with type 1 diabetes mellitus who could be observed for one year after the start of treatment, 33 patients were identified. The response to GH treatment and GH dosage were comparable to the GHD patients who were not with type 1 diabetes mellitus at the start of treatment. In the GHD patients with type 1 diabetes mellitus, 11 adverse events were identified (1 event each of “headache,” “acute sinusitis,” “naevus,” “allergic reaction,” “contusion of chest wall,” “knee injury,” “foreign body on external eye,” “diabetic nephropathy and the beginning of diabetic retinopathy,” “hypoglycaemia,” “worsening of metabolic control,” and “acute pancreatitis”). Worsening of metabolic control was considered to be related to somatropin preparations by the physicians,

[20] Published literature in which PMDA concluded that there was a description regarding the safety at the time of administration of somatropin preparations in patients with diabetes mellitus among the literature retrieved (searched on December 27, 2021) by the following conditions: (1) to (3).

(1) 94 published literature regarding clinical trials, meta-analysis, systematic review, and randomized controlled trials searched using PubMed with search formula [(somatropin OR GH OR hGH OR rhGH OR growth hormone) AND (diabet*) AND (safety OR adverse reaction)].
(2) 89 published literature searched using PubMed with search formula [(KIGS OR KIMS) AND (diabet*)].
(3) 127 published literature searched using Ichushi with search formula [(糖尿病/TH OR 糖尿病/AL) AND ((成長ホルモン/TH OR 成長ホルモン/AL) OR (Somatropin/TH OR ソマトロピン/AL)) AND ((副作用/TH OR 副作用/AL) OR (有害事象/TH OR 有害事象/AL) OR (安全性/TH OR 安全性/AL))] .

and the GH dosage was reduced. Regarding adverse events other than the worsening of metabolic control, a causal relationship was ruled out by the physicians. A serious adverse event was one acute pancreatitis. However, a causal relationship was ruled out by the physicians.

5.2 Clinical practice of growth hormone replacement therapy in Japanese patients with adult growth hormone deficiency: A postmarketing, multicenter, observational study of Growject (Endocrinology, diabetology & metabolism 2018; 47: 150-68)

A use-result survey was performed on all the cases seen and administered with Growject in their routine appointments in 71 clinics of 64 medical institutions where AGHD specialists were available. 235 cases were included in the safety analysis. 11 cases had concurrent or past diabetes mellitus (including borderline cases) in the investigation. No exacerbation of diabetes mellitus was observed in 10 cases, excluding 1 borderline one who developed diabetes mellitus following administration of a somatropin preparation.

5.3 A case of diabetes mellitus exacerbated during growth hormone (GH) replacement therapy for severe adult growth hormone deficiency (AGHD) in which replacement therapy was discontinued (Diabetes 2018; 61: S-255)

Male in his 20s. The patient was diagnosed with craniopharyngioma at the age of age 2. He continued GH treatment for panhypopituitarism after 2 surgeries and gamma-knife treatment at the of age 3. During the course of the disease, he gained weight and borderline diabetes developed, with a history of hospitalization. During his outpatient visits, he gained weight again and his casual blood glucose level rose to 400 mg/dL. GH treatment was discontinued and oral treatment with SGLT2 inhibitor, etc. was initiated, but the patient was hospitalized for treatment due to poor control. On admission, his body mass index (BMI) was 41 and a fatty liver was observed. The patient was managed on a 1,600-kcal diabetic diet, and on the 25th day of admission, he lost approximately 4 kg, and his casual blood glucose level improved to approximately 120 mg/dL, and he was discharged from the hospital.

5.4 Study regarding the effects of growth hormone replacement therapy on the glucose metabolism after 1 year in patients with severe adult growth hormone

deficiency (Diabetes Frontier 2017; 28: 594-8)

A retrospective observational study was performed in 9 patients (3 and 6, with or without concurrent diabetes mellitus, respectively) with severe AGHD having concurrent hypopituitarism that examined effects of GH treatment on glucose metabolism. Changes in fasting blood glucose levels observed after 1 year of treatment were the primary endpoint. Results indicated an increase of fasting blood glucose with GH treatment in all the patients (the mean fasting blood glucose level before and after 1 year of treatment was 96.6 mg/dL and 106.4 mg/dL, respectively ($p = 0.042$, Mann-Whitney U test)). In the 3 patients with concurrent diabetes mellitus, no changes in diet, exercise, and the drug treatment were observed and no significant increases were noted in the HbA1c (the HbA1c before and after 1 year of treatment was 6.07% and 6.35%, respectively ($p = 0.403$, Mann-Whitney U test)) although their fasting blood glucose levels were higher after GH treatment.

5.5 2 cases of safe and effective long-term growth hormone replacement therapy for severe adult growth hormone deficiency (aGHD) complicated by type 2 diabetes mellitus (The Japanese journal of endocrinology 2016; 92: 340)

- Case 1

  A 72-year-old female. The patient developed type 2 diabetes mellitus at the age of 65. She was admitted to the hospital around the age of 67 due to aggravation of malaise and depressed mood that did not improve even with increased hydrocortisone dosage. She was diagnosed with severe AGHD, and GH treatment was initiated. Rapid improvement in QOL was observed, and visceral fat reduction (visceral fat area on visceral fat CT scan decreased from 182 cm^2 to 157 cm^2) was also observed after 1 year of treatment. The patient's HbA1c was in the 6% range and her blood glucose control was good without oral antidiabetic medication 5 years after the start of treatment.

- Case 2

  A 69-year-old male. The patient has had diabetes mellitus complicated by hypertension since his 50s. He developed myocardial infarction at the age of 63. In the same year, the patient had cerebral infarction accompanied by bilateral internal carotid artery stenosis, which was complicated by pituitary apoplexy. His HbA1c rose to 9% with loss of strength and energy, requiring temporary insulin therapy. While on antidiabetic medication, he was hospitalized at the age of 69 years because he had difficulty even in going up a hill.

The patient was diagnosed with AGHD and started GH treatment, which improved his QOL and increased his physical activity. No change in antidiabetic medication was made in the first 3 months of the treatment, and his HbA1c improved from 6.8% to 6.1%, which has been maintained for the last 5 years.

5.6 Effects on insulin sensitivity and body composition of combination therapy with GH and IGF1 in GH deficient adults with type 2 diabetes (Eur J Endocrinol 2012; 167: 697-703)

A randomized placebo-controlled study was conducted to evaluate the effect on insulin sensitivity and body composition of combination therapy with GH and insulin-like growth factor-1 (hereinafter referred to as “IGF-1”) in AGHD patients with type 2 diabetes mellitus. Among 14 AGHD patients with type 2 diabetes mellitus, eight patients were randomized to GH and IGF-1 treatment group and six to GH and placebo treatment group. As a result, one malaise and alcohol abuse occurred as an adverse event in the GH and IGF-1 treatment group. Therefore, the relevant two patients dropped out from the clinical study at 3 months. Twelve patients in total completed the 6 months study; 6 patients in the GH and IGF-1 treatment group, and 6 patients in the GH and placebo treatment group. Positive effects on insulin sensitivity and body composition were observed in the GH and IGF-1 group. Tonsillitis occurred in 1 patient (treatment group unknown); however, no other adverse events were observed.

5.7 The effect of growth hormone (GH) replacement therapy in adult patients with type 1 diabetes mellitus and GH deficiency (Clin Endocrinol (Oxf) 2003; 58: 309-15)

An open-label intervention study was conducted for six months to evaluate the effects of GH treatment on the onset of retinopathy, metabolic parameters (diabetes mellitus control, insulin requirement, and frequency of hypoglycaemia and severity), etc. in 5 AGHD patients with type 1 diabetes mellitus. As a result, 5 patients all completed 6 months treatment, and no significant adverse events were noted during the study. Diabetes mellitus control remained stable after the GH treatment (mean ± standard error of the mean of HbA1c before the treatment and 6 months after the treatment was 8.2 ± 0.2% and 8.0 ± 0.4% respectively ($p = 0.9$, ANOVA), and it was necessary to increase the dose of insulin per day (mean ± standard error of the mean of insulin dose before the treatment and 6 months after the

treatment was 0.40 ± 0.09 U/kg/day, 0.70 ± 0.08 U/kg/day, respectively (p<0.04, ANOVA)). On the other hand, the frequency of severe hypoglycaemia (<3 mmol/L) decreased significantly (mean ± standard error of the mean of the incidence of severe hypoglycaemia one week before the treatment and 6 months after the treatment was 4.4 ± 1.4%, 1.8 ± 1.2%, respectively (p<0.04, paired t-test (two-sided)). Also, monthly eye photographs revealed no changes in the retina in any patients during the study.

5.8 Diabetes Mellitus in a Patient with Aarskog Syndrome on Growth Hormone Treatment (Clin Pediatr Endocrinol 1996; 5: 143-5)

Twelve-Year-old boy. He had Aarskog syndrome[21] with concurrent diabetes mellitus. GH was started in November 1994 at a dose of 0.5 IU/kg/week. Urinary glucose was noticed one month later, and hyperglycaemia was evident in January 1995. Though GH therapy was stopped immediately, his urinary glucose persisted even 4 months after cessation of GH therapy. An OGTT showed a diabetic pattern (50 g OGTT performed in July 1995 showed 90 mg/dL, 208 mg/dL, 211 mg/dL, 133 mg/dL at 0 minute, 30 minutes, 60 minutes, and 180 minutes, respectively). A diet therapy resulted in only slight hyperglycaemia and improved glucose tolerance. However, because growth velocity was very low at 1 cm/year, GH treatment was started again in June 1995. One month after initiation of GH, his urinary glucose excretion was 3 to 5 g/day, and fasting blood glucose remained normal.

6. Post-marketing surveillance

The results of the post-marketing surveillance including patients with concurrent diabetes mellitus administered with somatropin preparations were as follows.

6.1 Use-results survey for Growject in Japan

A use-results survey to investigate efficacy and safety after administration of Growject to AGHD patients was conducted in Japan from October 2009 to September 2015.

Among 235 cases subjected to safety analysis, 6 cases had concurrent diabetes mellitus. No adverse events occurred in each of the 6 cases.

[21] Genetic (x-linked recessive) disorders characterized by short stature and multiple facial, limb and genital abnormalities (cited from National Organization for Rare Disorders, Inc. website https://rarediseases.org/rare-diseases/aarskog-syndrome/ (accessed 27, December, 2021))

6.2 Specified use-results survey for Norditropin in patients with AGHD (only in severe cases)

A specified use-results survey of Norditropin to investigate efficacy, safety and other information on proper use of drugs in AGHD patients was conducted in Japan from October 2009 to December 2014.

Among 334 cases subjected to safety analysis, 1 case had concurrent diabetes mellitus. An adverse event of benign pituitary tumour, which was regarded as serious by a physician, occurred in the patient[22].

6.3 A non-interventional study of Norditropin in "short stature without epiphyseal closure associated with Turner's syndrome" and "GHD without epiphyseal closure"

A non-interventional study was conducted in Japan from May 2005 to June 2015 to evaluate the effectiveness, safety, and other proper use information of Norditropin in patients with short stature without epiphyseal closure associated with Turner's syndrome and GHD without epiphyseal closure.

Of the 2 045 cases subjected to safety analysis (168 cases with short stature without epiphyseal closure associated with Turner's syndrome and 1 877 cases with GHD without epiphyseal closure), 5 patients (all with GHD without epiphyseal closure) had concurrent diabetes mellitus

5 patients did not develop any adverse events deemed serious by their physicians.

6.4 Non-interventional study of Genotropin in pediatric patients with growth disorders such as idiopathic GHD, SGA short stature, and Turner syndrome

A non-interventional study (KIGS) was conducted from 1987 to 2012 to evaluate the long-term safety and treatment outcomes of Genotropin in pediatric patients with growth disorders, such as idiopathic GHD, SGA short stature, and Turner syndrome. 52 countries/regions, including Japan, participated in the study.

Of the 83 803 cases subjected to safety analysis, 421 cases had concurrent diabetes mellitus. Of these, 5 adverse events with an outcome of death were reported in 5 cases (3 events in 3 cases of death and 1 event in 1 case each of hypoglycemia and respiratory failure).

[22] The case is the same with one described in No.10 of Appendix 3.

In all of these events, the reporting physicians or the marketing authorization holder of Genotropin ruled out a causal relationship with Genotropin. In 421 cases with concurrent diabetes mellitus, no serious diabetes mellitus with significantly inadequate control[23] was observed.

10 Japanese patients with concurrent diabetes mellitus were included in the study, and no adverse drug reactions with an outcome of death were observed in these patients.

6.5 The genetics and neuroendocrinology of short stature International study (GeNeSIS)

An international collaborative post-marketing study to evaluate the effectiveness and safety of somatropin preparations[24] in pediatric patients with short stature was conducted from March 1999 to September 2015. 30 countries/regions, including Japan, participated in the study.

Of the 22 311 cases enrolled in the study and administered with somatropin preparations, 69 cases had diabetes mellitus as a complication or a history. Of the 69 cases, there were 5 adverse events with an outcome of death in 2 cases (2 events of cerebrovascular accident, 1 event each of brain stem infarction, diabetic ketoacidosis, and MELAS syndrome). In both cases, the reporting physicians and the marketing authorization holder of Humatrope ruled out a causal relationship with somatropin preparations.

Of the 69 cases whose complications or histories included diabetes mellitus, 3 serious adverse events related to glucose metabolism[24] were observed in 3 cases (1 event each of diabetic ketoacidosis, diabetic ketosis, and inadequately controlled diabetes mellitus"). In all of these cases, the reporting physicians and the marketing authorization holder of Humatrope ruled out a causal relationship with somatropin preparations.

1 Japanese patient with concurrent diabetes mellitus was included in the study, and no adverse drug reactions with an outcome of death or serious adverse drug reactions related to glucose metabolism[25] were observed in this patient.

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[23] On the basis of a "serious adverse event or reaction" defined in ICH E2D Guideline (PFSB/SD Notification No.0328007 Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting, dated March 28, 2005), the adverse reactions corresponded to those which the physician or the marketing authorization holder of Genotropin considered as serious and whose names (PT) fell under "Inadequately controlled diabetes mellitus."

[24] In principle, Humatrope was used. However, it was possible to administer other somatropin preparations temporarily when Humatrope cannot be administered.

6.6 Post-marketing safety study in AGHD patients (HypoCCS)

An international collaborative post-marketing study was conducted to investigate the prevalence and incidence of diabetes mellitus after administration of somatropin preparations[24] in AGHD patients between January 1996 and December 2012. 18 countries/regions including Japan, participated in the study.

Of the 8 716 cases in which somatropin preparations were administered in this investigation, the cases with at least 1 confirmed visit to the hospital were 8 420 cases. Of the 8 420 cases, 652 cases had diabetes mellitus as complications or past history. Of the 652 cases, 33 adverse events with an outcome of death occurred in 31 cases (3 events each of myocardial infarction and death, 2 events each of acute myocardial infarction, cardiac arrest, cardiac failure, and cerebrovascular accident, 1 event each of alcohol poisoning, cardiopulmonary failure, cardio-respiratory arrest, chronic obstructive pulmonary disease, metastatic colon cancer, coronary artery dissection, end stage renal disease, gastrointestinal haemorrhage, intracranial haemorrhage, hepatic encephalopathy, hypoglycaemia, invasive breast carcinoma, multiple organ dysfunction syndrome, myocardial ischaemia, acute pancreatitis, pneumonia, aspiration pneumonia, sepsis, and septic shock), and a causal relationship between all of these events and somatropin preparations was ruled out by the physician and marketing authorization holder of Humatrope.

Of the 652 patients whose complications or past history included diabetes mellitus, 20 serious adverse events related to glucose metabolism[25] were noted in 20 cases (7 events of hypoglycaemia, 4 events of hyperglycaemia, 2 events each of hypoglycaemic coma and type 2 diabetes mellitus, 1 event each of diabetes mellitus, inadequately controlled diabetes mellitus, diabetic coma, diabetic hyperosmolar coma, and diabetic hyperosmolar nonketotic syndrome). Of these events, the events for which the physicians or marketing authorization holder of Humatrope or both considered that a causal relationship between these events and somatropin preparations could not be ruled out were 2 events in 2 cases each of

[25] On the basis of a "serious adverse event or reaction" defined in ICH E2D Guideline (PFSB/SD Notification No.0328007 Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting, dated March 28, 2005), the adverse events/reactions corresponded to those which the physician or the marketing authorization holder of Humatrope considered as serious and whose names (PT) fell under "diabetes mellitus," "inadequately controlled diabetes mellitus," "diabetic coma," "diabetic hyperosmolar coma," "diabetic hyperosmolar nonketotic syndrome ," "diabetic ketoacidosis," "diabetic ketosis," "hyperglycaemia," "hypoglycaemia," "hypoglycaemic coma," "type 2 diabetes mellitus", "increased blood glucose", "decreased blood glucose", "impaired glucose tolerance", "increased glycosylated haemoglobin," and "type 1 diabetes mellitus."

hyperglycaemia and type 2 diabetes mellitus.

In this investigation, 11 Japanese patients with concurrent type 2 diabetes mellitus were included. Of the 11 cases, no adverse reactions with an outcome of death or serious adverse reactions related to glucose metabolism[25] were noted.

7. PMDA's judgement based on the investigation results

7.1 Decision on the administration to patients with diabetes mellitus

PMDA decided that patients with diabetes mellitus may be reasonably removed from the CONTRAINDICATIONS section of the precautions of somatropin preparations based on the following:

- All somatropin preparations have been contraindicated in patients with diabetes mellitus since the time of initial approval. While drugs for diabetes mellitus were limited in 1988 when the first somatropin preparation was approved (only a few insulin preparations, sulfonylureas, biguanides, and mesoxalic acid calcium[26] were approved in Japan (Latest Internal Medicine System 7, Metabolic diseases 2 (diabetes mellitus) Nakayama Shoten;1995, etc.)), options for diabetic treatment have increased since then at present (The Treatment Guide for Diabetes Mellitus 2020-2021 edited by the Japan Diabetes Society), so have, it is considered, patients with diabetes mellitus under adequate control. For indications of somatropin preparations, such as AGHD, on the other hand, no other options than GH treatment are available.
- Overseas (the US, EU, Canadian, and Australian) package inserts, clinical practice guidelines (including the GRS Consensus Guidelines in which the Japan Endocrine Society participates) and standard textbooks do not contraindicate administration of somatropin preparations to patients with diabetes mellitus, requiring special caution instead.
- In the cases of adverse reactions reported in Japan, serious adverse reactions related to glucose metabolism were found as observed following administration of somatropin preparations to patients with diabetes mellitus. Such serious adverse reactions have been reported as eventually improved and adequately controlled by temporal discontinuation of somatropin preparation or initiation of antidiabetic drugs in some cases. In addition, published literature discussing the safety of administration of

[26] Marketing was discontinued as of 2021.

somatropin preparations to patients with concurrent diabetes mellitus, as well as Japanese and overseas post-marketing surveillance studies, have reported many cases of patients with concurrent diabetes mellitus in which exacerbation of diabetes mellitus was not observed following administration of somatropin preparations.

7.2 Precautions regarding patients with diabetes mellitus, with glucose intolerance, or with risk factors of diabetes mellitus

If patients with diabetes mellitus are removed from the CONTRAINDICATIONS section, PMDA still considers that precautions be required regarding patients with diabetes mellitus, with glucose intolerance, or with risk factors of diabetes mellitus. Specifically, requirements should be noted for close monitoring of patients through adequate control and periodic measurements of blood glucose, HbA1c, etc. before and during administration of somatropin preparations, respectively, as well as dosage adjustment of antidiabetic drugs and other proper measures. PMDA cited the following as the reasons for such precautions:

- The pharmacological effects of somatropin preparations that may elevate blood glucose levels associated with the reduction in insulin sensitivity could deteriorate conditions of diabetes mellitus.
- Cases of adverse reactions have been reported in Japan in which a causal relationship between the adverse reactions related to glucose metabolism observed following administration of somatropin preparations and the drugs was reasonably possible.
- Clinical practice guidelines and standard textbooks overseas recommend against administering somatropin preparations to patients with concurrent inadequately controlled diabetes mellitus and the Canadian package insert of Genotropin notes “patients with Prader-Willi syndrome who have inadequately controlled diabetes” as a contraindication for the drug. Therefore, adequate control and monitoring of diabetes mellitus before and during administration of somatropin preparations, respectively, are considered to be important.
- Careful monitoring is also considered to be necessary in patients with glucose intolerance or with risk factors of diabetes mellitus similar to those with concurrent diabetes mellitus, based on the overseas package inserts and the GRS Consensus Guidelines which state that patients with glucose intolerance or with risk factors of diabetes mellitus should be closely monitored since previously undiagnosed diabetes

mellitus may be unmasked following administration of somatropin preparations.

PMDA also considers that a cautionary statement regarding co-administration with antidiabetic drugs should be added to the Precautions for Co-administration section because of the dose adjustment of antidiabetic drugs expected in administration of somatropin preparations to patients with concurrent diabetes mellitus who are receiving antidiabetic drugs.

Furthermore, concerning the periodic measurement of HbA1c, etc. mentioned in the IMPORTANT PRECAUTIONS section that should be preferably made because glucose tolerance may be reduced, the current statement varies among the preparations in the indications and details of the precautionary measures. PMDA considers that with the pharmacological effects of somatropin preparations, the risk of diabetes mellitus could not be ruled out in any patients regardless of their indications. Therefore, it is preferable to standardize the details of required monitoring and procedure for any abnormalities observed. PMDA decides that the details of the periodic measurement of blood glucose, HbA1c, or other parameters and procedure for any abnormalities observed in the IMPORTANT PRECAUTIONS section should be basically the same across different somatropin preparations.

7.3 Decision on administration and precaution in patients with concurrent proliferative or severe nonproliferative (preproliferative) diabetic retinopathy

Among patients with concurrent diabetes mellitus, those with proliferative or severe nonproliferative (preproliferative) diabetic retinopathy are noted as a contraindication in the US, Canadian, and Australian package inserts of somatropin preparations, certain overseas guidelines (American Association of Clinical Endocrinologists and American College of Endocrinology (AACE) Guidelines (2019)) and European Society for Paediatric Nephrology (ESPN) Guidelines (2019)), as well as overseas standard textbooks.

PMDA recognizes the possibility for somatropin preparations, with their proliferative effect, to exacerbate conditions of diabetic retinopathy. On the other hand, PMDA also expects the risks of the effects of somatropin preparations on diabetic retinopathy to be more limited under the proper monitoring by coordination of an ophthalmologist, endocrinologist, and pediatrician than expected at the initial approval taking into account the following:

- No consensus has been reached regarding administration of somatropin preparations in patients with proliferative or severe nonproliferative (preproliferative) diabetic retinopathy, which is contraindicated in the US, Canadian, and Australian package inserts, certain overseas guidelines, and overseas standard textbooks while not in the EU package inserts and the GRS Consensus Guidelines.
- While IGF-1 has been reported as being involved in the pathogenesis and progress of diabetic retinopathy (Eye 2020; 34(Suppl 1): 1-51, etc.), non-involvement of GH treatment in the retinal conditions has been also reported (J Clin Endocrinol Metab 2000; 85: 634-6, etc.).
- Contribution of GH to the development of diabetic retinopathy was reported in the past (Diabetes Care 1994; 17: 531-4) and the AACE Guidelines contraindicated administration in patients with diabetic retinopathy in 2003, which led to the listing of patients with proliferative or severe nonproliferative (preproliferative) diabetic retinopathy as a contraindication in the US package inserts of somatropin preparations in 2004 and thereafter based on the guidelines' decision. At present, however, it has been reported that vascular endothelial growth factor (VEGF) is the most significant among the factors driving diabetic retinopathy (VEGF, IGF-1, hepatocyte growth factor (HGF), basic fibroblast growth factor (b-FGF), etc.) (Eye 2020; 34(Suppl 1): 1-51), and actually, anti-VEGF agents have become the most widely adopted treatment of diabetic retinopathy (The Clinical Guidelines for Diabetic Retinopathy (1st edition), Committee for Clinical Guidelines, the Japanese Society of Ophthalmic Diabetology) .

Given the above considerations, PMDA intends to conclude on the appropriateness of administration in patients with proliferative or severe nonproliferative (preproliferative) diabetic retinopathy based on the expert discussion.

Of note, the following is the current treatment environment of diabetic retinopathy in Japan in which the procedure of monitoring and treatment for patients with proliferative or severe nonproliferative (preproliferative) diabetic retinopathy is considered to be established.

- Upon diagnosis with diabetes mellitus, instructing patients to visit monthly for proliferative retinopathy and bi-monthly for severe nonproliferative diabetic retinopathy is required (The Treatment Guide for Diabetes Mellitus 2020-2021 edited by the Japan Diabetes Society) indicating a consensus on periodic examination reached among

endocrinologists who administer somatropin preparations.

- Retinal photocoagulation therapy, etc. is available to inhibit or delay the progression of retinopathy for proliferative or severe nonproliferative diabetic retinopathy (The Treatment Guide for Diabetes Mellitus 2020-2021 edited by the Japan Diabetes Society, The Clinical Guidelines for Diabetic Retinopathy (1st edition), Committee for Clinical Guidelines, the Japanese Society of Ophthalmic Diabetology).

IV. Expert discussion

1. Decision on administration to patients with diabetes mellitus

The PMDA's decision to remove patients with diabetes mellitus from the CONTRAINDICATIONS section (see 7.1) was supported by all the expert advisors.

2. Precaution regarding patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus

The PMDA's decision mentioned in 7.2 was supported by all expert advisors. The decision that details of the periodic measurement of blood glucose, HbA1c, or other parameters and procedure for any abnormalities observed in the IMPORTANT PRECAUTIONS section be the same basically across somatropin preparations was supported by all the exert advisors. The following opinions were expressed by the advisors:

- Among the indications of somatropin preparations, Prader-Willi syndrome and Turner syndrome are more likely to have diabetes mellitus concurrently than other indications. Precaution is necessary concerning particularly close monitoring of the clinical course required for Prader-Willi syndrome and Turner syndrome.

A cautionary statement regarding impaired glucose tolerance that may concurrently occur in Turner syndrome particularly and close monitoring required for the event is already in place in the precautions for some somatropin preparations. The prevalence of concurrent type 2 diabetes mellitus has been reported as approximately 10%[10] for Turner syndrome and approximately 20%[9] for Prader-Willi syndrome.

Based on the above, PMDA decided that a cautionary statement is necessary with standardized language for all the somatropin preparations with different indications that impaired glucose tolerance may occur concurrently and close monitoring of the clinical

course is required in patients with Prader-Willi syndrome and Turner syndrome.

3. Decision on administration and precaution in patients with concurrent proliferative or severe nonproliferative (preproliferative) diabetic retinopathy

PMDA decided, based on the discussion mentioned in 7.3, that patients with proliferative or severe nonproliferative (preproliferative) diabetic retinopathy may not be noted in the CONTRAINDICATIONS section in the package inserts of somatropin preparations, and the decision was supported by all expert advisors with the following expert opinions expressed:

- Since administration of somatropin preparations will be allowed concurrently with treatment of diabetes mellitus, in order to remind clinical practice of the caution additionally required for diabetic complications, language concerning testing related to diabetic complications should be included in the precautions.
- In the general healthcare environment for diabetes mellitus, the requirement of instructing patients to visit ophthalmologists specified in the Treatment Guide for Diabetes Mellitus is not always adhered to. Physicians who provide treatment with somatropin preparations, on the other hand, are versed with professional knowledge and expertise in endocrine diseases including diabetes mellitus and are supposed to very rarely fail to adhere to the treatment guide. Nonetheless, to ensure that they instruct patients to see ophthalmologists when necessary, a reminder should be added to the precautions.
- Clinical practice has failed in the past to adhere to its duty of instructing patients with diabetes mellitus to visit ophthalmologists. The clinical guideline of diabetic retinopathy had to be revised to include a guide for intervals of visits by patients to ophthalmologists and be widely notified to clinical practice. In addition, it is known that progression to proliferative diabetic retinopathy is generally quick in young individuals (The Clinical Guidelines for Diabetic Retinopathy (1st edition), Committee for Clinical Guidelines, the Japanese Society of Ophthalmic Diabetology). Since young individuals without epiphyseal closure are included in patients who will receive somatropin preparations, requirement for close monitoring should be noted as a precaution.

PMDA concluded that a cautionary statement should be added to the Careful Administration or PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC

BACKGROUNDS section that diabetic complications (such as diabetic retinopathy) should be controlled and carefully monitored before and after initiation of administration, respectively, with somatropin preparations in patients with diabetes mellitus.

V. Overall evaluation

PMDA concluded that the precautions may be revised according to Appendix 5 (Appendix 5 is not included here. See the detailed information on Revisions of PRECAUTIONS.)

Appendix 1

Brand name	Marketing authorization holder	Indications/Dosage and administration
Growject Subcutaneous injection 6 mg, 12 mg, Growject for Injection 8 mg, Growject BC for injection 8 mg	JCR Pharmaceuticals Co., Ltd.	Growth hormone-deficient short stature without epiphyseal closure The usual dosage is 0.175 mg/kg of somatropin (genetical recombination) every week given as an intramuscular injection in 2 to 4 divided doses, or as a subcutaneous injection in 6 to 7 divided doses. Short stature without epiphyseal closure associated with Turner's syndrome The usual dosage is 0.35 mg/kg of somatropin (genetical recombination) every week given as an intramuscular injection in 2 to 4 divided doses, or as a subcutaneous injection in 6 to 7 divided doses. Adult growth hormone deficiency (only in severe cases) The usual dosage is 0.021 mg/kg of somatropin (genetical recombination) every week as an initial dose given as a subcutaneous injection in 6 to 7 divided doses. The dose is gradually increased according to the patient's conditions not exceeding 0.084 mg/kg a week, given as a subcutaneous injection in 6 to 7 divided doses. The dose should be adjusted depending on the patient's clinical symptoms and the results of the laboratory tests including serum concentrations of insulin-like growth factor-1 (IGF-1). The daily dose should not exceed 1 mg. Short stature without epiphyseal closure in patients born SGA (small-for-gestational age) The usual dosage is 0.23 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. If there is a lack of efficacy, the dose should be escalated up to 0.47 mg/kg a week given as a subcutaneous injection in 6 to 7 divided doses.
Genotropin TC Inj. 5.3	Pfizer Japan Inc.	Growth hormone-deficient short stature without epiphyseal closure

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Brand name	Marketing authorization holder	Indications/Dosage and administration
mg, 12 mg, Genotropin GoQuick Inj. 5.3 mg, 12 mg, and the others		The usual dosage is 0.175 mg/kg of somatropin (genetical recombination) every week given as an intramuscular injection in 2 to 4 divided doses, or as a subcutaneous injection in 6 to 7 divided doses. Short stature without epiphyseal closure associated with the following diseases Turner's syndrome The usual dosage is 0.35 mg/kg of somatropin (genetical recombination) every week given as an intramuscular injection in 2 to 4 divided doses, or as a subcutaneous injection in 6 to 7 divided doses. Chronic renal failure The usual dosage is 0.175 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. The dose may be escalated up to 0.35 mg/kg if the criteria for dose escalation are met after more than 6 months since the initiation of administration. Prader-Willi syndrome The usual dosage is 0.245 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. Adult growth hormone deficiency (only in severe cases) The usual dosage is 0.021 mg/kg of somatropin (genetical recombination) every week as an initial dose given as a subcutaneous injection in 6 to 7 divided doses. The dose is gradually increased according to the patient's conditions not exceeding 0.084 mg/kg a week, given as a subcutaneous injection in 6 to 7 divided doses. The dose should be adjusted depending on the

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Brand name	Marketing authorization holder	Indications/Dosage and administration
		patient's clinical symptoms and the results of the laboratory tests including serum concentrations of insulin-like growth factor-1 (IGF-1). The daily dose should not exceed 1 mg. Short stature without epiphyseal closure in patients born SGA (small-for-gestational age) The usual dosage is 0.23 mg/kg of Somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. If there is a lack of efficacy, the dose should be escalated up to 0.47 mg/kg a week given as a subcutaneous injection in 6 to 7 divided doses.
Norditropin FlexPro 5 mg, 10 mg, 15 mg	Novo Nordisk Pharma Ltd.	1. Growth hormone-deficient short stature without epiphyseal closure The usual dosage is 0.175 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. 2. Short stature without epiphyseal closure associated with Turner's syndrome The usual dosage is 0.35 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. 3. Short stature without epiphyseal closure associated with chondrodystrophy The usual dosage is 0.35 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. 4. Adult growth hormone deficiency (only in severe cases) The usual dosage is 0.021 mg/kg of somatropin (genetical recombination) every week as an initial dose given as a subcutaneous injection in 6 to 7 divided doses. The dose is gradually increased according to the patient's conditions not exceeding 0.084 mg/kg a week, given as a subcutaneous injection in 6 to 7 divided doses. The dose should be adjusted depending on the patient's clinical symptoms and the results of the laboratory tests including

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Brand name	Marketing authorization holder	Indications/Dosage and administration
		serum concentrations of insulin-like growth factor-1 (IGF-1). The daily dose should not exceed 1 mg. 5. Short stature without epiphyseal closure in patients born SGA (small-for-gestational age) The usual dosage is 0.23 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. If there is a lack of efficacy, the dose should be escalated up to 0.47 mg/kg a week given as a subcutaneous injection in 6 to 7 divided doses. 6. Short stature without epiphyseal closure associated with Noonan syndrome The usual dosage is 0.23 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. If there is a lack of efficacy, the dose should be escalated up to 0.47 mg/kg a week given as a subcutaneous injection in 6 to 7 divided doses.
Humatrope for injection 6 mg, 12 mg	Eli Lilly Japan K.K.	Growth hormone-deficient short stature without epiphyseal closure The usual dosage is 0.175 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. Short stature without epiphyseal closure associated with Turner's syndrome The usual dosage is 0.35 mg/kg of somatropin (genetical recombination) every week given as a subcutaneous injection in 6 to 7 divided doses. Short stature without epiphyseal closure associated with chondrodystrophy (achondroplasia, hypochondroplasia) The usual dosage is 0.35 mg/kg of somatropin (genetical recombination) every week given as a

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Brand name	Marketing authorization holder	Indications/Dosage and administration
		subcutaneous injection in 6 to 7 divided doses. Adult growth hormone deficiency (only in severe cases) The usual dosage is 0.021 mg/kg of somatropin (genetical recombination) every week as an initial dose given as a subcutaneous injection in 6 to 7 divided doses. The dose is gradually increased according to the patient's conditions not exceeding 0.084 mg/kg a week, given as a subcutaneous injection in 6 to 7 divided doses. The dose should be adjusted depending on the patient's clinical symptoms and the results of the laboratory tests including serum concentrations of insulin-like growth factor-1 (IGF-1). The daily dose should not exceed 1 mg.

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Appendix 2

Descriptions in overseas package inserts concerning administration to patients with diabetes mellitus

1. Descriptions in US package insert

Genotropin (somatropin) for injection, for subcutaneous use	Norditropin (somatropin) for injection, for subcutaneous use	Humatrope (somatropin) for injection, for subcutaneous use
January 2020 version	March 2020 version	October 2019 version
Contraindications Diabetic Retinopathy Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy. **Warnings and precautions** Impaired Glucose Tolerance and Diabetes Mellitus Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and	**Contraindications** Active proliferative or severe non-proliferative diabetic retinopathy. **Warnings and precautions** Glucose Intolerance and Diabetes Mellitus Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. New onset type 2 diabetes mellitus has been reported in patients taking somatropin. Previously undiagnosed impaired glucose	**Contraindications** Active proliferative or severe non-proliferative diabetic retinopathy. **Warnings and precautions** Glucose Intolerance and Diabetes Mellitus Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. New onset type 2 diabetes mellitus has been reported in patients taking somatropin. Previously undiagnosed impaired glucose

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Genotropin (somatropin) for injection, for subcutaneous use	Norditropin (somatropin) for injection, for subcutaneous use	Humatrope (somatropin) for injection, for subcutaneous use
overt diabetes mellitus may be unmasked during somatropin treatment. New-onset Type 2 diabetes mellitus has been reported. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral/injectable agents) may require adjustment when somatropin therapy is instituted in these patients.	tolerance and overt diabetes mellitus may be unmasked. Monitor glucose levels periodically in all patients receiving Norditropin, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely. The doses of antidiabetic agents may require adjustment when Norditropin is initiated.	tolerance and overt diabetes mellitus may be unmasked. Monitor glucose levels periodically in all patients receiving Humatrope, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely. The doses of antidiabetic agents may require adjustment when Humatrope is initiated.

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Genotropin (somatropin) for injection, for subcutaneous use	Norditropin (somatropin) for injection, for subcutaneous use	Humatrope (somatropin) for injection, for subcutaneous use
Drug Interactions Insulin and/or Oral/Injectable Hypoglycemic Agents In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable agent may require adjustment when somatropin therapy is initiated [see Warnings and Precautions].	**Drug Interactions** Insulin and/or Other Hypoglycemic Agents Clinical Impact：Treatment with Norditropin may decrease insulin sensitivity, particularly at higher doses. Intervention：Patients with diabetes mellitus may require adjustment of their doses of insulin and/or other hypoglycemic agents [see Warnings and Precautions].	**Drug Interactions** Insulin and/or Other Hypoglycemic Agents Clinical Impact：Treatment with Humatrope may decrease insulin sensitivity, particularly at higher doses. Intervention：Patients with diabetes mellitus may require adjustment of their doses of insulin and/or other hypoglycemic agents [see Warnings and Precautions].

2. Descriptions in EU package inserts

Genotropin/Genotonorm (somatropin), 1.3 mg, 5.0 mg, 5.3 mg, or 12 mg, powder and solvent for solution for injection	Norditropin FlexPro (somatropin) 5 mg/1.5 ml, 10 mg/1.5 ml, or 15 mg/1.5 ml, solution for injection in pre-filled pen	Humatrope (somatropin) 6 mg, 12mg, or 24mg, powder and solvent for solution for injection
October 2021 version	May 2021 version	July 2021 version
Special warnings and precautions for use *Insulin sensitivity* Somatropin may reduce insulin sensitivity. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during somatropin therapy. *Small for gestational age* In SGA children it is recommended to measure fasting insulin and blood glucose before start of treatment and annually	Special warnings and precautions for use *Blood glucose and insulin* In Turner syndrome and SGA children it is recommended to measure fasting insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk of diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans), oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, somatropin should not be administered. Somatropin has been found to influence	Special warnings and precautions for use Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted. Patients with diabetes or glucose intolerance should be monitored closely during somatropin therapy. In children born SGA it is recommended to measure fasting plasma insulin and blood glucose before start of treatment and

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Genotropin/Genotonorm (somatropin), 1.3 mg, 5.0 mg, 5.3 mg, or 12 mg, powder and solvent for solution for injection	Norditropin FlexPro (somatropin) 5 mg/1.5 ml, 10 mg/1.5 ml, or 15 mg/1.5 ml, solution for injection in pre-filled pen	Humatrope (somatropin) 6 mg, 12mg, or 24mg, powder and solvent for solution for injection
thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered.	carbohydrate metabolism, therefore, patients should be observed for evidence of glucose intolerance. *Insulin sensitivity* Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance (see section Interaction with other medicinal products and other forms of interaction). For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin containing product therapy is instituted. Patients with diabetes or glucose intolerance should be monitored closely during somatropin therapy.	annually thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered until the patient has been stabilised for diabetes care. Then growth hormone may be introduced with careful monitoring of the diabetic metabolic control. An increase in insulin dosage may be required.

Genotropin/Genotonorm (somatropin), 1.3 mg, 5.0 mg, 5.3 mg, or 12 mg, powder and solvent for solution for injection	Norditropin FlexPro (somatropin) 5 mg/1.5 ml, 10 mg/1.5 ml, or 15 mg/1.5 ml, solution for injection in pre-filled pen	Humatrope (somatropin) 6 mg, 12mg, or 24mg, powder and solvent for solution for injection
Interaction with other medicinal products and other forms of interaction Also see section Special warnings and precautions for use for statements regarding diabetes mellitus and thyroid disorder.	Interaction with other medicinal products and other forms of interaction In insulin treated patients adjustment of insulin dose may be needed after initiation of somatropin treatment (see section Special warnings and precautions for use).	Interaction with other medicinal products and other forms of interaction Patients with diabetes mellitus who receive concomitant somatropin may require adjustment of their doses of insulin and/or other anti-hyperglycaemic agents.

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

3. Descriptions in Canadian package inserts

Genotropin GoQuick (somatropin)	Norditropin NordiFlex (somatropin)	Humatrope(somatropin) 6 mg, 12 mg, or 24 mg powder and solvent for solution for injection
July 2020 version	July 2021 version	September 2021 version
Contraindications Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy. Genotropin is contraindicated in patients with Prader-Willi syndrome who have uncontrolled diabetes, or active psychosis, or have active cancer. Warnings and Precautions *Serious Warnings and Precautions* Therapy with Genotropin should be excluded for pediatric patients with Prader- Willi syndrome who have one or more of the	Contraindications Growth hormone should not be administered in patients with proliferative or preproliferative diabetic retinopathy. Warnings and Precautions *Endocrine and Metabolism* Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. New onset type 2 diabetes mellitus has been	Contraindications Somatropin should not be administered to patients with active proliferative or severe nonproliferative diabetic retinopathy. Warnings and Precautions *Endocrine and Metabolism:* Patients with diabetes mellitus or glucose intolerance should be monitored closely during therapy with somatropin, as an

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Genotropin GoQuick (somatropin)	Norditropin NordiFlex (somatropin)	Humatrope(somatropin) 6 mg, 12 mg, or 24 mg powder and solvent for solution for injection
following risk factors: uncontrolled diabetes, active cancer, active psychosis. *Endocrine and Metabolism* Patients with diabetes mellitus or glucose intolerance should be monitored closely during therapy with somatropin, as an adjustment of their antidiabetic therapy may be required. Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in patients with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus, those receiving high dose corticosteroid therapy, and patients with impaired glucose tolerance or pre-existing diabetes mellitus. As a result,	reported in patients taking somatropin. Previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus. Patients with pre-existing type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral/injectable agents) may require adjustment when somatropin therapy is	adjustment of their antidiabetic therapy may be required (see Monitoring and Laboratory Tests). Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in patients with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus, those receiving high dose corticosteroid therapy, and patients with impaired glucose tolerance or pre-existing diabetes mellitus. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, patients who receive somatropin should be monitored for evidence of

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Genotropin GoQuick (somatropin)	Norditropin NordiFlex (somatropin)	Humatrope(somatropin) 6 mg, 12 mg, or 24 mg powder and solvent for solution for injection
previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, patients who receive somatropin should be monitored for evidence of abnormal glucose metabolism and/or diabetes mellitus. New-onset type 2 diabetes mellitus has been reported in children and adults receiving somatropin.	instituted in these patients. *Monitoring and Laboratory Tests* Because human growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance. Patients with diabetes or glucose intolerance should be monitored closely during therapy with growth hormone. In Turner syndrome and SGA children it is recommended to measure fasting insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk of diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be	abnormal glucose metabolism and/or diabetes mellitus. New-onset type 2 diabetes mellitus has been reported in children and adults receiving somatropin.

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Genotropin GoQuick (somatropin)	Norditropin NordiFlex (somatropin)	Humatrope(somatropin) 6 mg, 12 mg, or 24 mg powder and solvent for solution for injection
Drug Interactions *Insulin and/or Oral/Injectable Hypoglycemic Agents* In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable agent may require adjustment when somatropin therapy is initiated (see WARNINGS AND PRECAUTIONS).	performed. If overt diabetes occurs, somatropin should not be administered. Drug Interactions *Drug-Drug Interactions* Insulin and/or Oral Hypoglycemic Agents Effects：May decrease effectiveness of insulin and/or hypoglycemic agents Clinical comments：Dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated.	Drug Interactions *Drug-Drug Interactions* Insulin and Anti-hyperglycemic Agents Effects：Patients with diabetes mellitus who receive concomitant somatropin may require adjustment of their doses of insulin and/or other antihyperglycemic agents. Clinical comments：Because somatropin may induce a state of insulin resistance, patients who receive somatropin should be monitored for evidence of abnormal glucose metabolism and/or diabetes mellitus. New-onset type 2 diabetes mellitus has been

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Genotropin GoQuick (somatropin)	Norditropin NordiFlex (somatropin)	Humatrope(somatropin) 6 mg, 12 mg, or 24 mg powder and solvent for solution for injection
		reported in children and adults receiving somatropin.

4. Descriptions in Australian package inserts

Genotropin and Genotropin GoQuick (somatropin) powder for injection with diluent (with preservative)	Norditropin SimpleXx and Norditropin FlexPro (somatropin) injection solution	Humatrope (somatropin) powder for injection
February 2020 version	April 2021 version	January 2019 version
	Contraindications Growth hormone is contraindicated in patients with proliferative or preproliferative diabetic retinopathy.	Contraindications Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.
Special warnings and precautions for use Somatropin reduces insulin sensitivity and therefore patients should be observed for evidence of glucose intolerance. In rare cases the diagnostic criteria for type 2 diabetes mellitus may be fulfilled as a result of growth hormone therapy but risk factors such as obesity (including obese PWS	Special warnings and precautions for use In SGA children it is recommended that fasting insulin and blood glucose be measured before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, Turner syndrome, severe insulin resistance, acanthosis nigricans), oral	Special warnings and precautions for use *Abnormal Glucose Metabolism and Diabetes Mellitus* Because somatropin may induce a state of insulin resistance, patients who receive somatropin should be observed for evidence of abnormal glucose metabolism and/or diabetes mellitus. New-onset type 2 diabetes

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Genotropin and Genotropin GoQuick (somatropin) powder for injection with diluent (with preservative)	Norditropin SimpleXx and Norditropin FlexPro (somatropin) injection solution	Humatrope (somatropin) powder for injection
patients), family history, steroid treatment or pre-existing impaired glucose tolerance have been present in most cases where this has occurred. Growth hormone can be used in patients with already manifest diabetes mellitus, however, its use requires special care and the dose of anti-diabetic therapy may require adjustment.	glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered.	mellitus has been reported in children and adults receiving somatropin. Patients with diabetes mellitus who receive concomitant somatropin may require adjustment of their doses of insulin and/or other anti-hyperglycaemic agents. *Children born SGA* In children born SGA it is recommended to measure fasting plasma insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (eg familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt

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Genotropin and Genotropin GoQuick (somatropin) powder for injection with diluent (with preservative)	Norditropin SimpleXx and Norditropin FlexPro (somatropin) injection solution	Humatrope (somatropin) powder for injection
Interactions with other medicines and other forms of interactions See also statements under SPECIAL WARNINGS AND PRECAUTIONS FOR USE regarding diabetes mellitus, thyroid disorder and ACTH deficiencies.		diabetes occurs growth hormone should not be administered until the patient has been stabilised for diabetes care. Then growth hormone may be introduced with careful monitoring of the diabetic metabolic control. An increase in insulin dosage may be required. Interactions with other medicines and other forms of interactions Patients with diabetes mellitus who receive concomitant somatropin may require adjustment of their doses of insulin and/or other anti-hyperglycaemic agents.

Appendix 3

List of cases with serious adverse reactions in Japan in patients with diabetes mellitus

No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administration and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
1	Genotropin	1996	14	Female	Hypopituitarism	Hypopituitarism, congenital aplastic anaemia, cardiomyopathy, type 1 diabetes mellitus, haemochromatosis, bone marrow transplant	Diabetic ketosis	Approximately 1 month	Discontinuation	Recovered by increasing the amount of insulin, etc.
		1996					Hyperglycaemia	Approximately 1 month	Discontinuation	Recovered by increasing the amount of insulin, etc.
2	Genotropin	1997	52	Female	Cardiac failure	Congestive cardiomyopathy, cardiac failure, ventricular arrhythmia, gastritis, diabetes mellitus, complete atrioventricular block, anaemia	Death	51 days	N/A	Transferred, but died
3	Genotropin	1998	62	Male	Cardiac failure	Congestive cardiomyopathy,	Myocardial infarction	10 days	Unknown	Transferred to the hospital by

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No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administration and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
						cardiac failure, ventricular arrhythmia, gastritis, peripheral arterial occlusive disease, atrial fibrillation, diabetes mellitus				ambulance, but died due to multi-organ failure
4	Humatrope	1999	14	Male	Growth hormone deficiency	Growth hormone deficiency, craniopharyngioma, atopic dermatitis, ergotherapy, hepatic steatosis, hyperlipidaemia, hypopituitarism, type 2 diabetes mellitus requiring insulin, medical diet, obesity, radiotherapy	Type 2 diabetes mellitus[*1]	Approximately 2 years and 4 months	Discontinuation	Recovering by the start of short-acting insulin, etc.
5	Genotropin	2002	17	Male	Height below the normal	Type 2 diabetes mellitus, height below	Type 2 diabetes mellitus[*1]	86 days	Discontinuation	Recovering by administration of

No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administration and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
					range	the normal range, Prader-Willi syndrome, hepatic steatosis				an oral antidiabetic drug (nateglinide)
6	HumatropeC[*2]	2007	53	Male	Growth hormone deficiency	Type 2 diabetes mellitus, growth hormone deficiency, adrenal insufficiency, hypertension, hyperlipidaemia, benign pituitary tumour, tobacco user	Type 2 diabetes mellitus	210 days	Discontinuation	Recovering by administration of oral antidiabetic drugs (glimepiride and metformin hydrochloride)
7	HumatropeC[*2]	2007	61	Female	Growth hormone deficiency	Growth hormone deficiency, hypopituitarism, hypothyroidism, adrenal insufficiency, diabetes mellitus, hepatitis C, hyperuricaemia, increased platelet count, increased white	Essential thrombocythaemia	153 days[*4]	Discontinuation	Aspirin was administered, and the patient temporarily recovered, but the symptoms subsequently recurred and the patient did not recover.

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No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administration and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
						blood cell count, hypothalamo-pituitary disorder				
8	Saizen[*3]	Un-known	17	Female	Off label use	Off label use, type 2 diabetes mellitus, diabetes insipidus, chemotherapy, radiotherapy, hypopituitarism, intellectual disability, hypothalamo-pituitary disorder, temperature regulation disorder, eating disorder, central obesity, epilepsy, hyperuricaemia	Diabetes mellitus	Unknown	The drug was temporarily withdrawn, and the treatment was resumed with reduced dose.	Treatment for the adverse reactions is unknown, the outcome was “recovering.”
9	HumatropeC[*2]	2009	81	Female	Growth	Type 2 diabetes	Hydrocephalus[*5]	Approximately	Continued	Unknown

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No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administration and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
					hormone deficiency	mellitus, hypertension, gastrooesophageal reflux disease, insomnia, diabetes insipidus, adrenal insufficiency, secondary hypothyroidism, constipation, hypercholesterolaemia		17 months		
10	Norditropin FlexPro	2013	40	Male	Growth hormone deficiency	Growth hormone deficiency, abnormal glucose tolerance, diabetes mellitus, non-secretory adenoma of pituitary, trans-sphenoidal hypophysectomy, hyperlipidaemia, non-alcoholic steatohepatitis	Recurrent pituitary tumour	766 days	Discontinuation	Recovered by additional surgery and gamma knife treatment

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No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administration and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
11	Norditropin FlexPro	2013	54	Male	Growth hormone deficiency	Growth hormone deficiency, type 2 diabetes mellitus, benign pituitary tumour, hypophysectomy, hyperlipidaemia, hypertension, liver disorder	Benign pituitary tumour	1 000 days	Discontinuation	Recovering by gamma knife treatment and extirpation
12	Norditropin FlexPro	2015	72	Female	Growth hormone deficiency	Type 2 diabetes mellitus, empty sella syndrome, growth hormone deficiency, secondary hypothyroidism, osteoporosis, supraventricular tachycardia, cardiac valve disease, large intestine polyp, diabetes insipidus, hypertension,	Adenocarcinoma of colon	72 days	Discontinuation	Recovering by colectomy

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No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administration and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
						insomnia, anxiety, gastrooesophageal reflux disease, gastric ulcer, uterine leiomyoma, lumbar vertebral fracture, back pain, intestinal diverticulum				
13	Saizen[*3]	Un-known	23	Male	Hypopituitarism	Diabetes mellitus, craniopharyngioma, tumour excision, postoperative hypopituitarism, diabetes insipidus, abnormal hepatic function, hepatic fibrosis, decreased platelet count	Diabetes mellitus	Unknown	Discontinuation	Unknown
		Un-known					Decreased appetite	Unknown	Discontinuation	Unknown
		Un-known					Malaise	Unknown	Discontinuation	Unknown
		Un-known					Insomnia	Unknown	Discontinuation	Unknown
14	Genotropin GoQuick	Un-known	Un-kno-wn	Female	Hypopituitarism	Diabetes mellitus, hypopituitarism	Seizure	Unknown	Unknown	Unknown
		2018					Loss of control of	2 days	Unknown	Unknown

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No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administration and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
							legs			
15	Unknown	Un-known	15	Un-known	Unknown	Diabetes mellitus, developmental delay, gait disturbance, hypoacusis, schizophrenia	Diabetes mellitus	Unknown	Unknown	Unknown
16	Norditropin FlexPro	2020	41	Female	Growth hormone hyposecretion	Growth hormone hyposecretion, depression, gestational diabetes, dietary control	Diabetes mellitus	204 days	Discontinuation	Unknown

*1: It was considered that a causal relationship between somatropin preparations and the adverse reactions was reasonably possible.
*2: Brand name of “HumatropeC” was changed to “Humatrope for injection” in December, 2008.
*3: Approval was withdrawn in April, 2021.
*4: Increased platelet count was observed before the start of administration of HumatropeC.
*5: Spontaneous report from the patient indicated that the patient had been told that water had accumulated in the head, however, details are unknown.

Appendix 4

List of cases with non-serious adverse reactions (events related to glucose metabolism) in Japan in patients with diabetes mellitus

No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administra-tion and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
1	Norditropin	2013	58	Fe-male	Growth hormone deficiency	Growth hormone deficiency, diabetes mellitus	Increased blood glucose	Unknown	Continued	Unknown
2	Unknown	Un-known	Adult	Male	Growth hormone deficiency	Growth hormone deficiency, diabetes mellitus	Diabetes mellitus	Unknown	Discontinuation	Treatment for the adverse reactions is unknown, the outcome was “recovered.”
3	Unknown	Un-known	Un-known	Un-known	Growth hormone deficiency	Growth hormone deficiency, diabetes mellitus	Diabetes mellitus	Unknown	Discontinuation	Unknown
4	Humatrope	Un-known	Un-known	Fe-male	Unknown	Depression, diabetes mellitus, visual field defect	Increased blood glucose	Unknown	Unknown	Unknown
5	Humatrope	Un-known	61	Fe-male	Unknown	Diabetes mellitus	Diabetes mellitus	Unknown	The drug was temporary withdrawn, and	Unknown

No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administra-tion and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
									resumed.	
6	Humatrope	Un-known	13	Fe-male	Growth hormone deficiency Nonalcoholic fatty liver disease	Autonomic nervous system imbalance, craniopharyngioma, diabetes insipidus, diabetes mellitus, hypothyroidism, insulin resistance, obesity, primary adrenal insufficiency	Insulin resistance	Unknown	Unknown	Unknown
		Un-known					Obesity	Unknown	Unknown	Unknown
7	Humatrope	Un-known	75	Fe-male	Growth hormone deficiency	Diabetes mellitus	Increased blood glucose	Unknown	Continued	Unknown
8	Genotropin	Un-known	63	Fe-male	Growth hormone deficiency	Diabetes mellitus, growth hormone deficiency, craniopharyngioma, hepatic steatosis, gallstones	Inadequately controlled diabetes mellitus[*1]	Unknown	Continued	Recovered by the start of administration of pioglitazone
9	Genotropin	Un-known	17	Fe-male	Unknown	Nongerminomatous germ cell tumour of	Diabetes mellitus	Unknown	The drug was temporarily	Recovered by diet therapy

No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administra-tion and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
						the CNS, diabetes insipidus, hypopituitarism, cerebellar atrophy, intellectual disability, hypothalamo-pituitary disorder, abnormal blood sodium, temperature regulation disorder, eating disorder, obesity, epilepsy, hyperuricaemia, type 2 diabetes mellitus, radiotherapy, surgery, growth hormone deficiency			withdrawn, and the treatment was resumed with reduced dose.	
10	Genotropin	Un-known	12	Male	Unknown	Diabetes mellitus, Obesity	Increased glycosylated haemoglobin	Unknown	Unknown	Unknown

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No.	Brand name	Year of onset	Age	Sex	Reason for administration of somatropin preparations	Underlying diseases/ complications/ past history	Adverse reactions (PT)	Period between administration and onset	Administration of somatropin preparations after the onset of adverse reactions	Treatment for the adverse reactions and outcomes
11	Unknown	Unknown	61	Female	Growth hormone deficiency	Diabetes mellitus, hypothyroidism, depression, suicide attempt, injury, hypopituitarism, growth hormone deficiency	Increased blood glucose	Unknown	Unknown	Unknown

*1: It was considered that a causal relationship between somatropin preparations and the adverse reactions was reasonably possible.