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Pharmaceuticals and Medical Devices Agency



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

Revision of Precautions

Somatropin (genetical recombination) (preparations indicated for growth hormone-deficient short stature without epiphyseal closure, short stature without epiphyseal closure associated with Turner's syndrome/chronic renal failure/Prader-Willi syndrome, adult growth hormone deficiency (only in severe cases), and short stature without epiphyseal closure in patients born SGA (small-for-gestational age))

April 4, 2022

Pharmaceuticals and Medical Devices Agency

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Therapeutic category

Pituitary hormone preparations

Non-proprietary name

Somatropin (genetical recombination)

Safety measure

Precautions should be revised in the package insert.

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Revision in line with the Instructions for Package Inserts of Prescription Drugs, PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau, MHW, dated April 25, 1997 (Old instructions): Revised language is underlined.

Current	Revision
<p>Contraindications</p> <p><u>Patients with diabetes mellitus (Growth hormone has anti-insulin-like effects.)</u></p> <p>Careful Administration</p> <p>(N/A)</p>	<p>Contraindications</p> <p>(deleted)</p> <p>Careful Administration</p> <p><u>Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus (In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA1c, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration. After initiation, levels of blood glucose, HbA1c, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic retinopathy). Doses of antidiabetic drugs should be adjusted when required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug. Patients with glucose intolerance or with risk factors of diabetes mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.)</u></p>

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Important Precautions

(N/A)

When this drug is administered to patients with short stature associated with Prader-Willi syndrome, clinical symptoms of underlying diseases should be carefully monitored through the following:

- 1) Absence of diabetes mellitus should be confirmed prior to administration of this drug through testing of blood glucose, HbA_{1c}, etc. Testing should be performed periodically during administration.
- 2) Spinal deformity (scoliosis) may progress excessively. Patients should be carefully monitored through periodic physical and x-ray examinations, etc. during administration.

Levels of blood glucose and HbA_{1c} may rise with administration of

Important Precautions

Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA_{1c} may rise with administration of this drug. Levels of blood glucose, HbA_{1c}, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken such as dose reduction or temporal discontinuation of this drug. Particularly in patients with Prader-Willi syndrome or Turner's syndrome, patients may become complicated with reduced glucose tolerance. Conditions of patients should be closely monitored.

When this drug is administered to patients with short stature associated with Prader-Willi syndrome, spinal deformity (scoliosis) may progress excessively. Patients should be carefully monitored through periodic physical and x-ray examinations, etc.

(deleted)

this drug in patients with adult growth hormone deficiency. Blood glucose, HbA_{1c}, urinary glucose, etc. should be measured periodically and dose reduction or discontinuation of administration should be considered if any abnormalities are observed.

Drug Interactions

Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Insulin	<u>Effects of insulin to lower blood glucose may be attenuated.</u>	<u>Growth hormone has anti-insulin-like effects.</u>

Drug Interactions

Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
<u>Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, etc.)</u>	<u>Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA_{1c}, etc. should be measured periodically and doses of these drugs should be adjusted.</u>	<u>Growth hormone reduces insulin sensitivity.</u>

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Adverse Reactions

Other Adverse Reactions

<Growth hormone-deficient short stature without epiphyseal closure, short stature without epiphyseal closure associated with the following diseases (Turner's syndrome, chronic renal failure or Prader-Willi syndrome), short stature without epiphyseal closure in patients born SGA (small-for-gestational age)>

Site	Adverse reactions
Endocrine system	Hypothyroidism, decreased TSH, reduced glucose tolerance ^{Note 3)}

Note3) Urinary glucose, HbA_{1c}, etc. should preferably be measured periodically.

<Adult growth hormone deficiency (only in severe cases)>

Site	Adverse reactions
Endocrine system	Hypothyroidism, reduced glucose tolerance ^{Note 3)} , dysmenorrhoea

Note3) Urinary glucose, HbA_{1c}, etc. should be preferably measured periodically.

Adverse Reactions

Other Adverse Reactions

<Growth hormone-deficient short stature without epiphyseal closure, short stature without epiphyseal closure associated with the following diseases (Turner's syndrome, chronic renal failure, Prader-Willi syndrome), short stature without epiphyseal closure in patients born SGA (small-for-gestational age)>

Site	Adverse reactions
Endocrine system	Hypothyroidism, decreased TSH, reduced glucose tolerance

(deleted)

<Adult growth hormone deficiency (only in severe cases)>

Site	Adverse reactions
Endocrine system	Hypothyroidism, reduced glucose tolerance, dysmenorrhoea

(deleted)

N/A: Not Applicable. No corresponding language is included in the current precautions.

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Revision in line with the Instructions for Electronic Package Inserts of Prescription Drugs, etc. PSEHB Notification No. 0611-1 by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 11, 2021 (New instructions): Revised language is underlined.

Current	Revision
<p>2. CONTRAINDICATIONS <Common to all indications> <u>Patients with diabetes mellitus (Growth hormone has anti-insulin-like effects.)</u></p> <p>8. IMPORTANT PRECAUTIONS <Common to all indications> <u>Glucose tolerance may be reduced. Levels of Urinary glucose, HbA_{1c}, etc. should be preferably measured periodically.</u></p> <p><Short stature without epiphyseal closure associated with Prader-Willi syndrome> <u>Symptoms of underlying diseases should be monitored as follows:</u> • <u>Absence of diabetes mellitus should be confirmed through testing</u></p>	<p>2. CONTRAINDICATIONS <Common to all indications> (deleted)</p> <p>8. IMPORTANT PRECAUTIONS <Common to all indications> <u>Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA_{1c} may rise with administration of this drug. Levels of blood glucose, HbA_{1c}, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug. Particularly in patients with Prader-Willi syndrome or Turner's syndrome, patients may become complicated with reduced glucose tolerance. The clinical course of patients should be closely monitored.</u></p> <p><Short stature without epiphyseal closure associated with Prader-Willi syndrome> Spinal deformity (scoliosis) may progress excessively. Patients should be carefully monitored through periodic physical and x-ray</p>

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of blood glucose, HbA_{1c}, etc. prior to administration. Testing should be performed periodically during administration.

- Spinal deformity (scoliosis) may progress excessively. Patients should be carefully monitored through periodic physical and x-ray examinations, etc.

<Adult growth hormone deficiency (only in severe cases)>

Levels of blood glucose and HbA_{1c} may rise with administration of this drug. Blood glucose, HbA_{1c}, urinary glucose, etc. should be measured periodically, and dose reduction or discontinuation of administration should be considered if any abnormalities are observed.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.1 Patients with Complication or History of Diseases, etc.

(N/A)

examinations, etc.

<Adult growth hormone deficiency (only in severe cases)>
(deleted)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.1 Patients with Complication or History of Diseases, etc.

Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus

In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA_{1c}, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration.

After initiation, levels of blood glucose, HbA_{1c}, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic

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retinopathy). Doses of antidiabetic drugs should be adjusted when required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug.

Patients with glucose intolerance or with risk factors of diabetes mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.

10. INTERACTIONS

10.2 Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Insulin	<u>Effects of insulin to lower blood glucose may be attenuated.</u>	<u>Growth hormone has anti-insulin-like effects.</u>

10. INTERACTIONS

10.2 Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
<u>Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1</u>	<u>Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and doses of these drugs should be adjusted.</u>	<u>Growth hormone reduces insulin sensitivity.</u>

	<u>receptor agonists,</u> <u>SGLT2 inhibitors,</u> <u>etc.)</u>		
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